

Soft Enolization: A Powerful Method for Diastereoselective Carbon-Carbon Bond Formation

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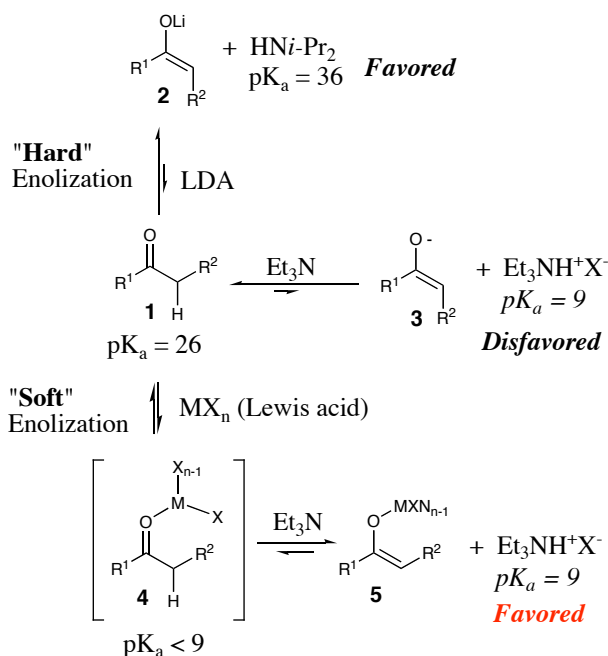
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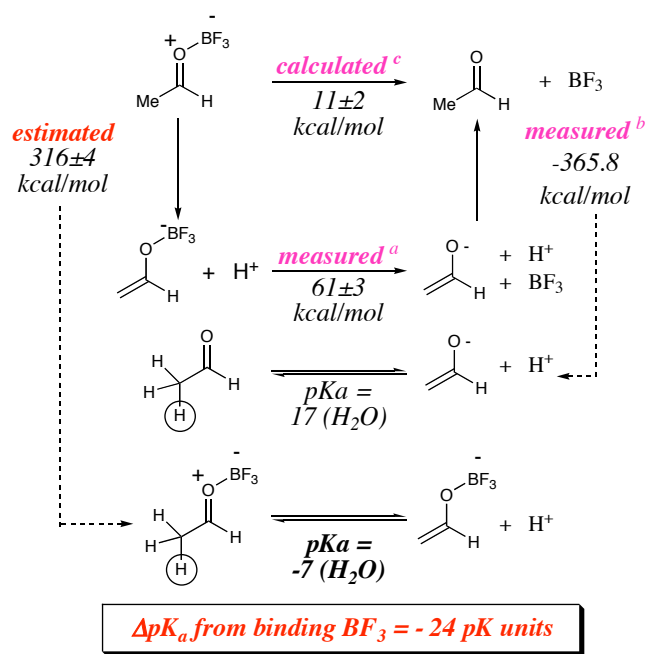
Introduction

Metal enolates are reactive nucleophiles employed in a variety of useful reactions.¹ Enolates are typically produced by deprotonation of a carbonyl compound with a strong base (Scheme 1).² The metal amide bases,³ such as lithium diisopropylamide (LDA), used for this process allow for complete deprotonation by virtue of the large difference in acidity of the carbonyl starting material and the secondary amine product. Consequently, weak bases are typically insufficient to produce useful quantities of the desired enolate intermediates. In the presence of a Lewis acid, however, deprotonation by the action of a weak base is possible, allowing for generation of metal enolates under mild conditions. The formation of a metal enolate through the use of a Lewis acid and a weak base has been termed "soft" enolization and has found wide application in stereoselective organic synthesis.



Scheme 1. "Hard" vs "Soft" Enolization. Values for pK_a are in DMSO except for HNi-Pr_2 which is in THF.

The empirical observations regarding the increased acidity of carbonyl α -protons are supported by *ab initio* calculations and thermochemical measurements. Ren *et al* employed flowing afterglow mass spectrometry to measure the binding energy of boron trifluoride (BF_3) to the enolate of acetaldehyde.⁴ This measurement was examined in conjunction with values for the binding of BF_3 to acetaldehyde (calculated) and the energy of deprotonation of acetaldehyde (measured) to estimate the change in acidity (ΔpK_a) of acetaldehyde bound to BF_3 (scheme 2). A calculated correction for solvation energy indicates that the ΔpK_a is approximately -24 pK units. This number correlates very well with our own empirical observation that the pK_a of commonly employed enolate precursors (ie ketones and imides) are reduced by at least 17 pK units in the presence of Lewis acids that are significantly milder than BF_3 .



Scheme 2: Ren's quantification of the acidity enhancement that BF₃ imparts to acetaldehyde. a) measured with energy-resolved collision-induced dissociation (CID) flowing afterglow mass spectrometry, b) calculated from the observed pK_a of acetaldehyde, c) *ab initio* calculations employing MP2, B3LYP, CBS, and CCSD(T) levels of theory.

The extreme utility of soft enolization originates from the ability of a variety of metals to participate in the process. Hard enolization generally produces alkali metal enolates.⁵ By virtue of the spherical symmetry of the participating atomic orbitals, alkali metal enolates cannot adopt defined geometries and thus exhibit limited stereocontrol in subsequent reactions.⁶ Moreover, substrates are limited by their ability to tolerate the enolization conditions. Soft enolization, on the other hand, can occur with a wide variety of metal centers, each of which confers complimentary properties to the resultant enolate (Figure 1). While enolates are formed from various transition metals and metalloids, the vast majority of selective reactions result from enolates of 4 metals: titanium, boron, tin(II) and magnesium. This review examines the properties of each of these metal enolates in detail and also describes very recent reactions involving the use of zinc and nickel complexes as catalysts.

Metals Commonly Employed For Soft Enolization

Other Metals That Facilitate Soft Enolization

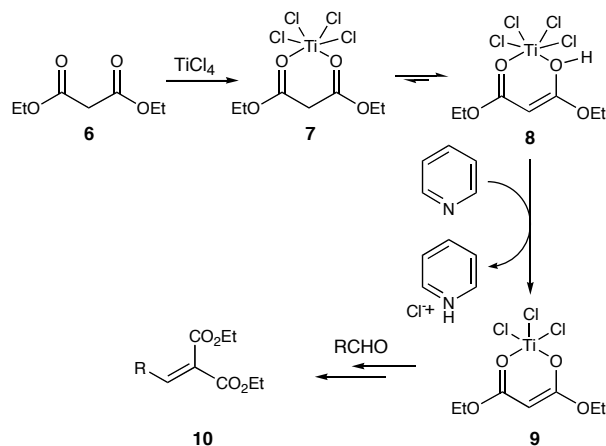
H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac	Lr	Rf	Db	Sg	Bh	Hs	Mt								

Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr

Figure 1. Summary of metals used for soft enolization.

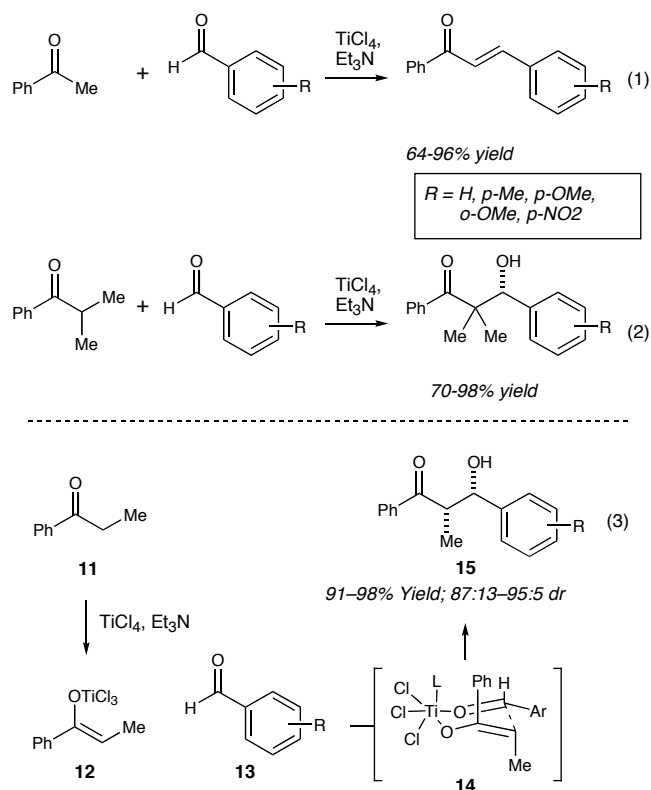
I. Titanium

Lehnert made an early observation which would later be described as proceeding by soft enolization.⁷ A Knoevenagel condensation was shown to proceed readily in the presence of titanium tetrachloride and pyridine as a base. Given the inability of pyridine to form the enolate of diester **6** in the absence of a metal additive, it is reasonable to assume that the process occurs *via* the intermediacy of titanium enolate **9**.



Scheme 2. Lehnert's titanium-mediated Knoevenagel condensation.

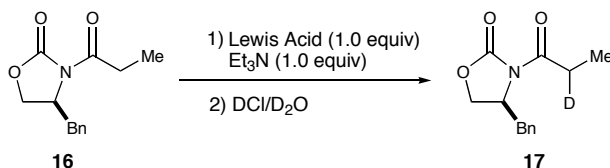
Subsequent to Lehnert's observation, there were several reports of generating titanium enolates by soft enolization. The first case in which aldol products were formed was reported by Harrison.⁸ While acetophenone produced only chalcones when combined with aromatic aldehydes in the presence of TiCl_4 and Et_3N (eq 1), propiophenone and isopropylphenyl ketone each gave high yields of aldol products (eqs 2 and 3). In the case of propiophenone (**11**), the reaction was highly syn-selective, by virtue of *Z*-enolate **12** that reacts through chair transition state **14**.



The degree to which titanium, and other metals, form enolates was investigated in detail by our group at the outset of our systematic study of titanium enolates.⁹ *N*-propionyloxazolidinone **16** was treated with a metal source, then triethylamine. The mixture was quenched with $\text{D}_2\text{O}/\text{DCl}$ and the degree of deuterium incorporation measured by ^1H NMR spectroscopy (table 1). TiCl_4 and $\text{Cl}_3\text{TiOi-Pr}$ formed enolates quantitatively when triethylamine was employed as base. Other metal sources exhibited varying degrees of enolization, while several sources (SnCl_4 , ZrCl_4 , and Et_2AlCl) showed no enolization, though the reason for their lack of reactivity is unclear. It was surprising to

find that $\text{MgBr}_2 \cdot \text{OEt}_2$ formed only 25% of the enolate, and this finding is discussed in detail later.

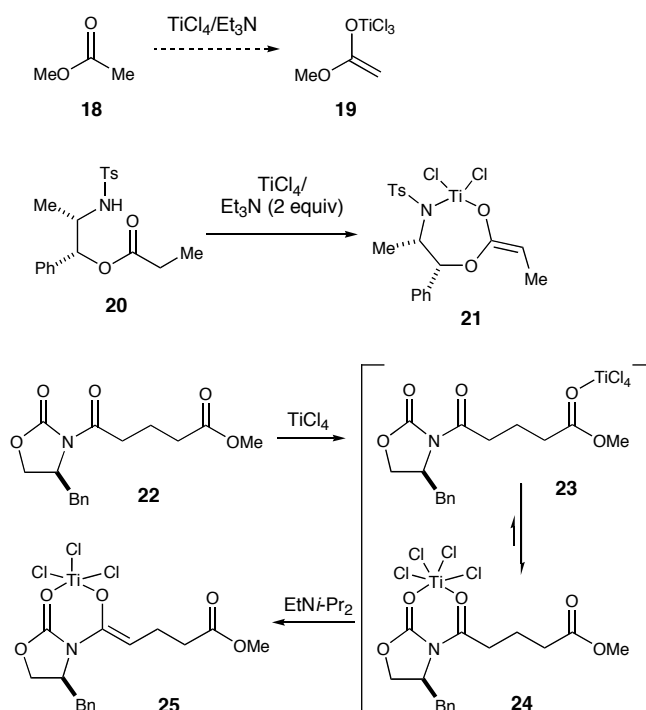
Table 1: Soft enolization with various metals



Lewis Acid	% deuterium
TiCl_4	100
$\text{TiCl}_3(\text{O}i\text{-Pr})$	100
$\text{TiCl}_4 \cdot (\text{THF})_2$	80
$\text{TiCl}_2(\text{O}i\text{-Pr})_2$	70
AlCl_3	70
$\text{MgBr}_2 \cdot \text{OEt}_2^*$	25
$\text{TiCl}(\text{O}i\text{-Pr})_3$	10
$\text{SnCl}_4, \text{Et}_2\text{AlCl}, \text{ZrCl}_4$	0

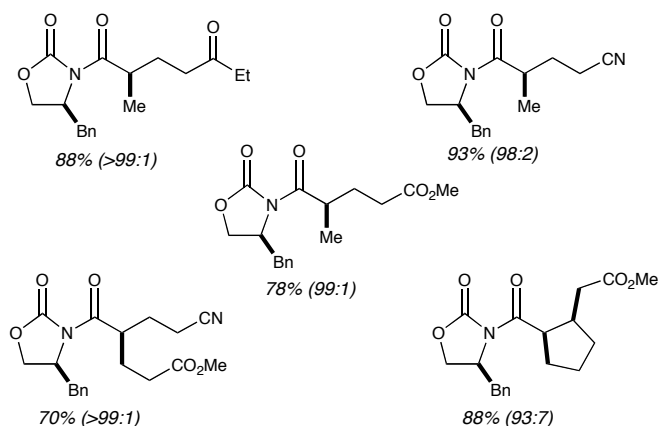
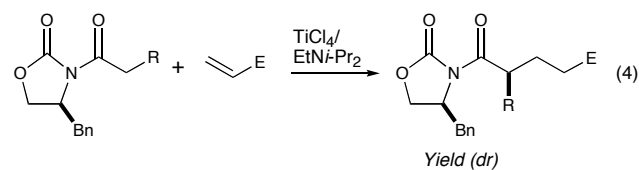
*2.0 equiv required

Chelating substrates are prone to enolization with TiCl_4 , even when the analogous monodentate substrate is resistant to enolization (Scheme 3). We have shown that methyl acetate **18** is not enolized by TiCl_4 under our standard conditions, yet enolization of chelating ester **20**, derived from norephedrine, is observed in the presence of two equivalents of base.¹⁰ Based on the observations with methyl acetate and propionyl oxazolidinone, it is not surprising that a γ -carbomethoxy oxazolidinone **22** is selectively enolized at the imide terminus. This finding further reinforces the utility of soft enolization, since a selective enolization of one carbonyl proton over the other with a metal amide base would be difficult.

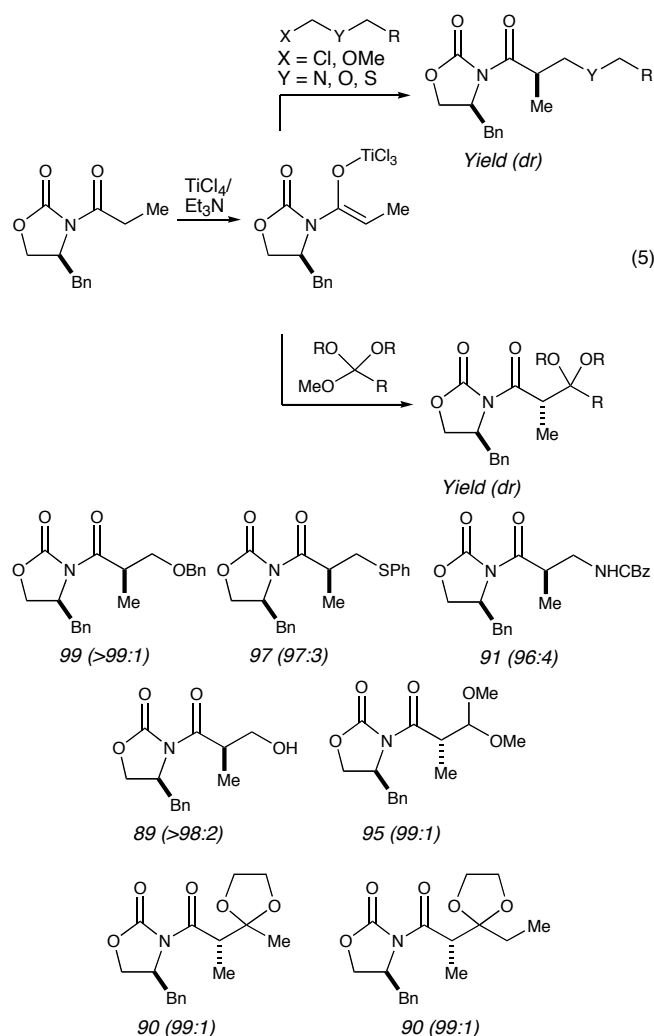


Scheme 3. Chelation facilitates soft enolization.

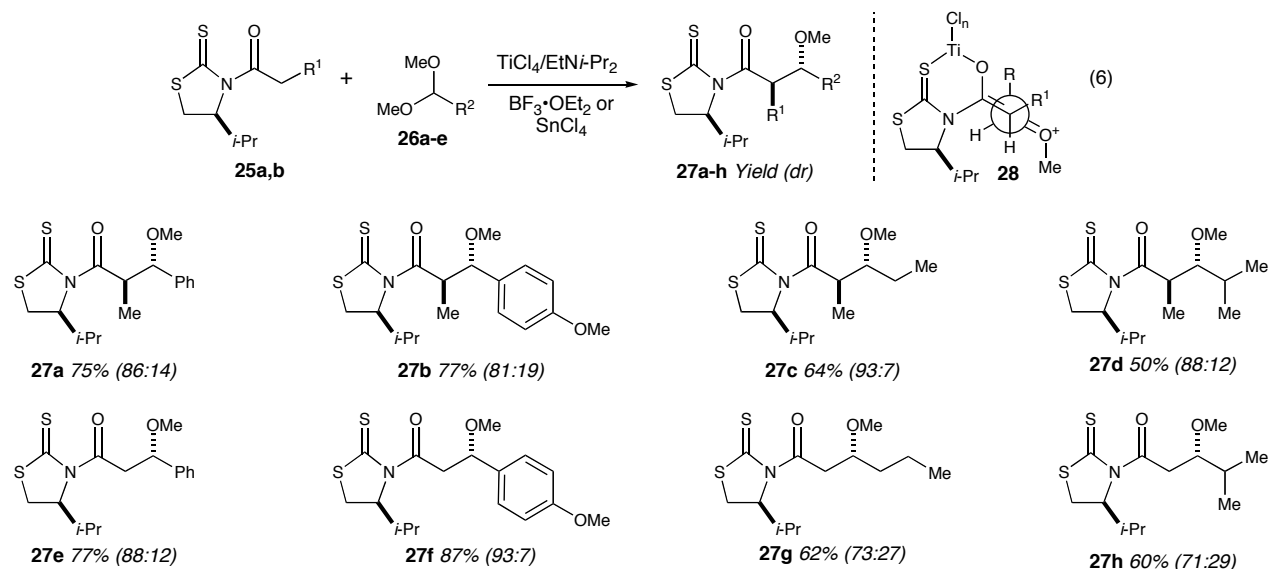
Chlorotitanium enolates formed through soft enolization are useful for a variety of stereoselective carbon-carbon bond-forming reactions. Stereoselective Michael reactions proceed with high selectivity for a variety of acceptors (eq 4).¹¹ The high chemoselectivity observed under enolization conditions with TiCl_4 and EtNi-Pr_2 allows for the preparation of a terminally differentiated symmetrical dicarboxylate synthon. Finally, an intramolecular variant allows for the highly stereoselective preparation of substituted cyclopentane.



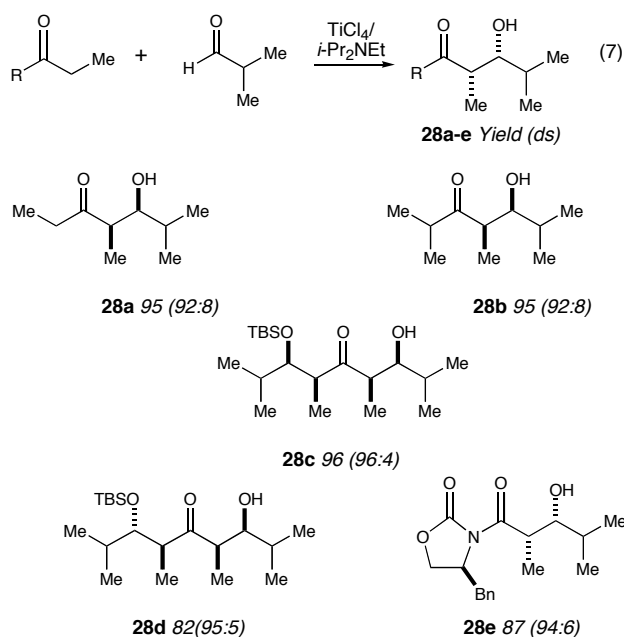
Titanium enolates are also useful nucleophiles for addition reactions with acetals and acetal equivalents (eq 5). Active methylene acetals react with high stereoselectivity to yield ethers, thioethers and substituted amides.¹² Trioxane also reacts to form the formaldehyde aldol product. Orthoformates and orthoacetates react to form acetal protected β -keto imide equivalents. In each case, a small amount of excess TiCl_4 is likely acting as a Lewis acid catalyst for these reactions.



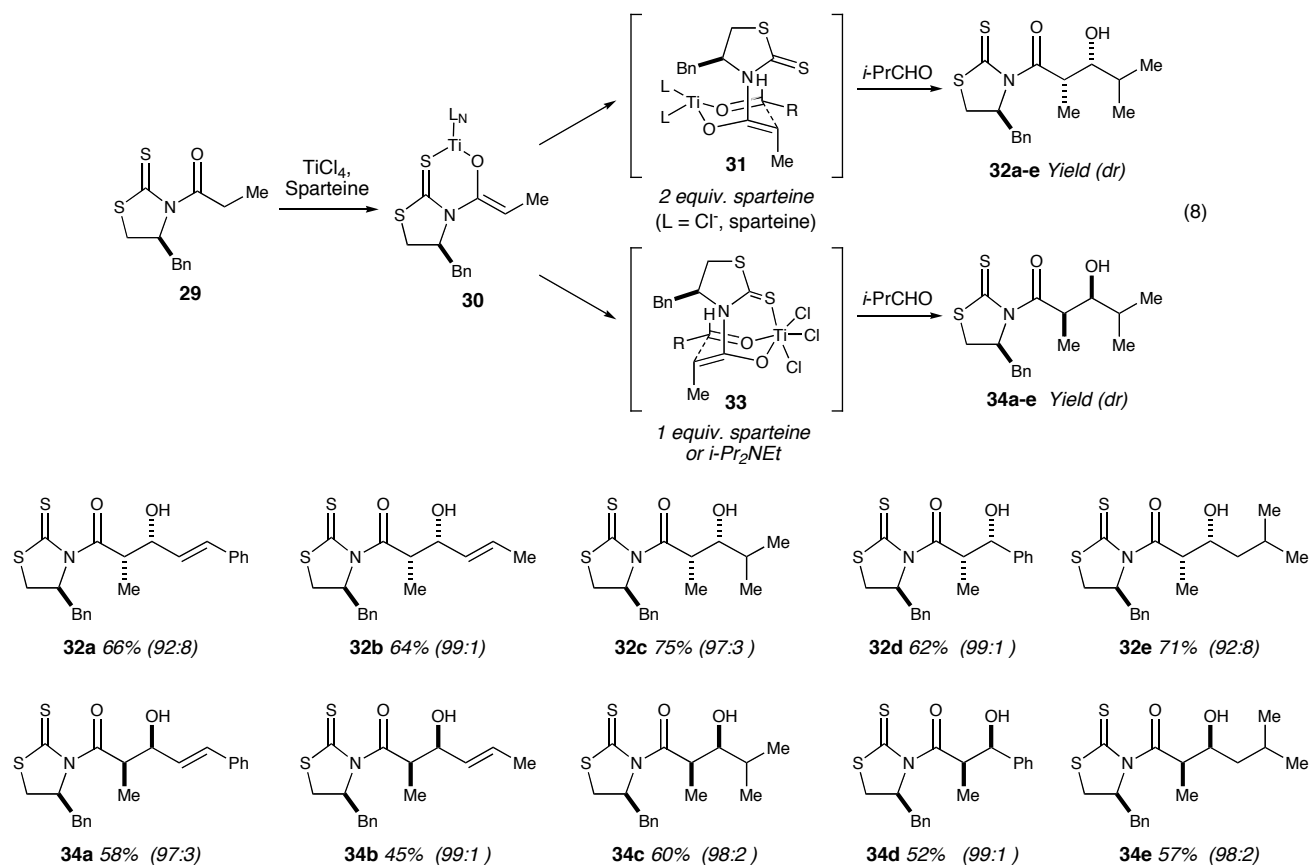
A variant of the orthoacetate reaction was developed by Urpí which employs methyl acetals and thus produces *O*-methyl aldol products (eq 6).¹³ Acetals are less reactive than orthoesters, so as a result a full equivalent of added Lewis acid is needed to form the oxonium ion that is attacked by the intermediate titanium enolate. Propionyl and acetyl thiazolidinethiones react with modest to high selectivity. The reaction is sensitive to the electronic properties of the acetal and an electron-rich aromatic rings can either increase (cf **27a** and **27b**) or decrease (cf **27e** and **27f**) the selectivity depending on the substitution of the acyl group. The stereoselectivity is adequately explained by open transition state **28**, which is reminiscent of that proposed by Heathcock in a Lewis acid-mediated boron aldol reaction (*vide infra*) that gives a similar stereochemical outcome.



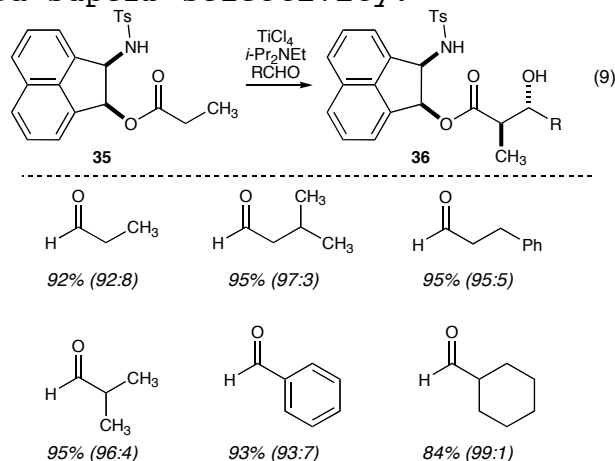
Titanium enolates are superb substrates for diastereoselective aldol reactions (eq 7).¹⁴ Ketones exhibit high syn selectivity which is likely the result of highly selective formation of a (*Z*)-enolate intermediate. In the case of chiral β -silyloxy ketones which yield products **28c** and **28d**, high stereochemical relay from the distal side of the ketone carbonyl is conferred to the enolate, allowing for an efficient iterative assembly of polypropionate synthons. In addition, the reaction is effective with oxazolidinone enolates with yields that rival the analogous reaction with Bu_2BOTf (*vide infra*), albeit with slightly reduced selectivity.



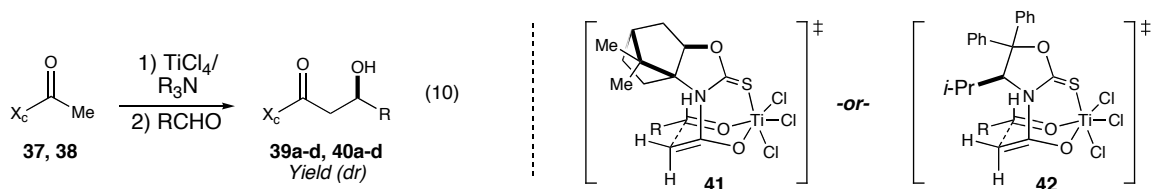
An extension of the TiCl_4 -mediated oxazolidinone aldol reaction which allows stereochemical reversal has recently been reported (eq 8).¹⁵ The use of standard enolization conditions with acyl thiazolidinethione **29** produces the complementary stereoisomer to that observed in the oxazolidinone aldol reaction (**28e**, eq 7). This stereochemical outcome is postulated to proceed through chair-like transition state **33** in which the exocyclic sulfur of the auxiliary binds to the titanium center. The use of multiple equivalents of base produces the same stereochemical outcome as observed in the oxazolidinone aldol reaction. This latter observation is believed to result from the base binding to the metal center, which prevents the exocyclic sulfur of the auxiliary from binding as it does in transition state **33**.¹⁶ Consequently, transition state **31** is operative and the selectivity is reversed. A similar stereochemical parity was observed by Yan with titanium and boron enolates of a camphor-derived auxiliary.¹⁷



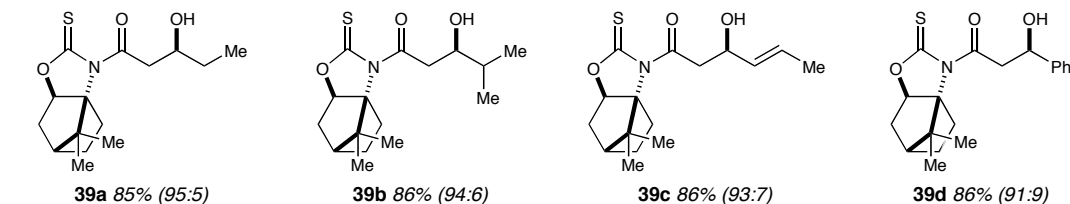
The first enantioselective anti aldol reaction was reported with titanium. Ghosh first reported that 1,2-aminoalcohol-derived ester auxiliaries would undergo anti aldol reactions with a variety of aldehydes.¹⁸ The first auxiliary was derived from aminoindanol, but Ghosh subsequently showed that 2-amino-1-acenaphthenol-based substrate **35** exhibited superb selectivity.¹⁹



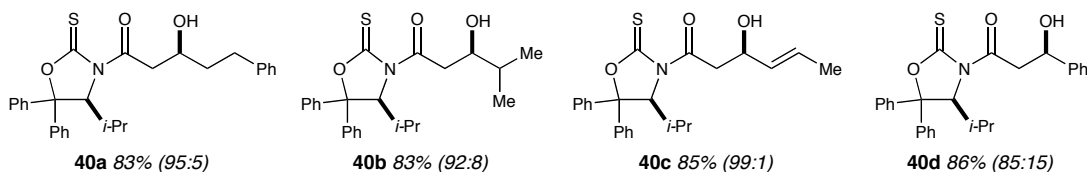
Use of titanium as the metal center for enolization has recently yielded a selective acetate aldol reaction (eq 10). While oxazolidinone auxiliaries are ineffective, the use of modified oxazolidine thione auxiliaries developed by Yan,²⁰ and subsequently Phillips,²¹ show high diastereoselectivity. The reaction works well for alkyl and aryl aldehydes and probably proceeds *via* chelated transition structures **41** and **42**. Similar reactions were reported by Nagao and Samakia using thiazolidinethione auxiliaries and $\text{Sn}(\text{OTf})_2$ or PhBCl_2 as metal sources respectively (*vide infra*).



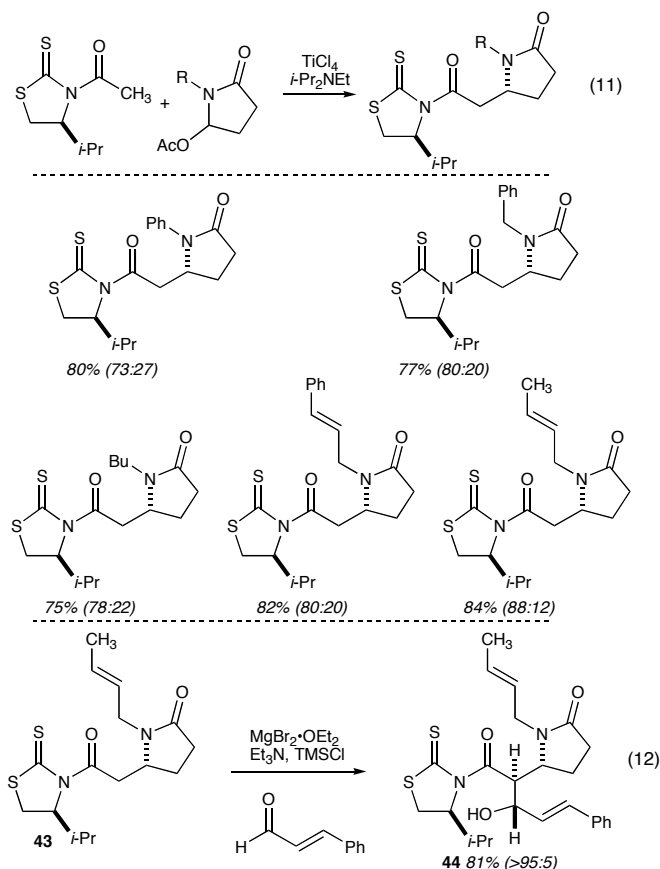
Yan ($R_3N = i\text{-Pr}_2\text{NEt}$):



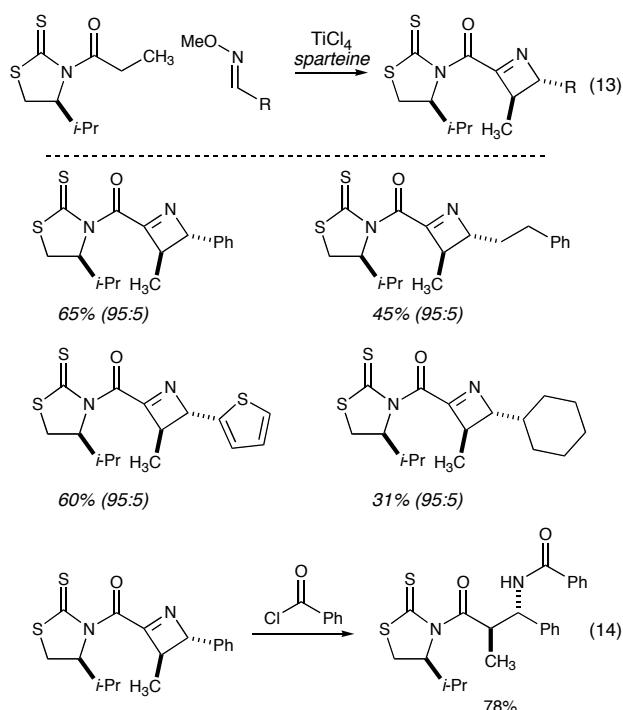
Phillips ($R_3N = \text{Sparteine}$):



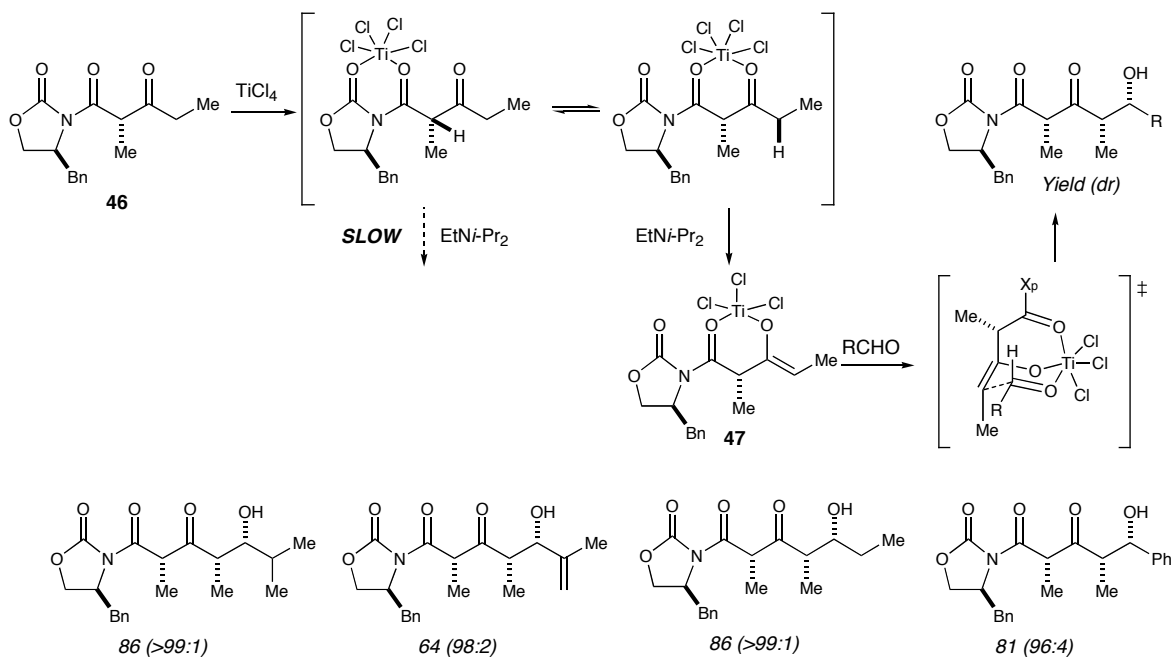
Thiazolidinethione enolates also undergo diastereoselective additions to *N*-acyl imminium ions (eq 11). Modest stereoinduction is observed, and in most cases the yield is good. While Olivo does not comment on the use of other auxiliaries, it is likely that higher selectivity is possible with more sterically demanding substrates. The products of the imminium ion addition are poised to undergo a second aldol addition (eq 12). When the Mg-catalyzed conditions reported by our group (*vide infra*) are employed, **43** reacts with cinnamaldehyde to produce aldol product **44** as a single diastereomer.



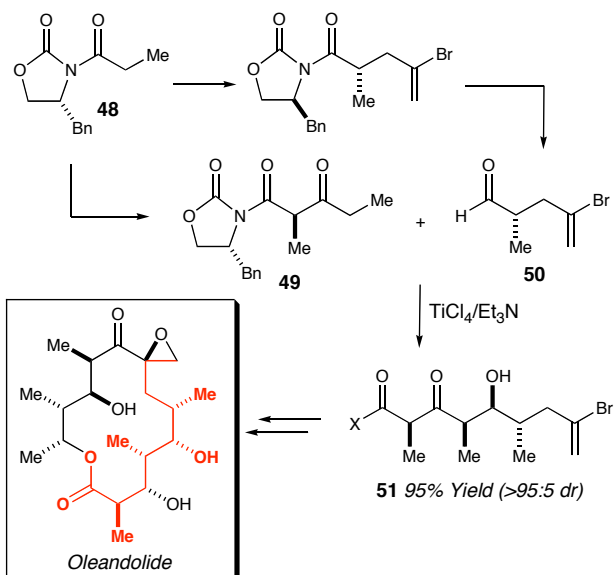
Titanium enolates have recently been shown to undergo several interesting reactions with imine electrophiles. Liotta demonstrated that a diastereoselective formal [2+2] process was observed when the titanium enolate of a thiazolidinethione was allowed to react with methyl oximes derived from various aldehydes (eq 13). Furthermore, the products could be hydrolytically opened with benzoyl chloride to provide protected β -amino acid derivatives (eq 14).



One of the most powerful reactions to emerge from our studies of soft enolization is the aldol reaction of β -keto imides (Scheme 4).²² The low kinetic acidity of the dicarbonyl proton of β -keto imides was noted in our original studies of lithium enolate acylation.²³ The stereochemical integrity of acylated imides was shown to persist under conditions that would normally cause epimerization of dicarbonyl compounds. This effect was attributed to the $A^{1,3}$ strain that develops between the auxiliary and the methyl group of the acyl unit during enolization. It was thus predicted that the external, and seemingly *less* acidic, carbonyl group of imide **46** would be enolized in preference to the dicarbonyl. This hypothesis was realized and the ensuing aldol reaction of titanium enolate **47** proceeded with high diastereoselection for the all syn diastereomer. A selective deprotonation of this nature would be impossible under conditions of hard enolization.

Scheme 4. Chemoselective enolization in the β -keto imide aldol reaction

The titanium mediated β -keto imide aldol reaction has been applied to a variety of challenging synthetic targets. The synthesis of oleandolide (Scheme 5) is particularly noteworthy in its efficient construction from readily available building blocks.²⁴ Aldehyde **50** was synthesized in 3 steps from imide **48**, then employed in a double-diastereodifferentiating aldol reaction with β -keto imide **49** to provide the stereotetrad **51** in 96% yield and >95:5 diastereoselectivity.

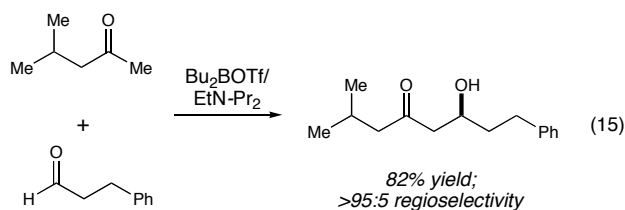


Scheme 5. Synthesis of oleandolide *via* the titanium-mediated β -keto imide aldol reaction.

Titanium enolates accessed through soft enolization show broad reactivity and high selectivity in a variety of reactions. The reaction scope for titanium enolates is broader than reactions based on soft enolization with any other metal. Diastereoselective alkylations, Michael reactions, and a variety of aldol reactions are possible. The high selectivity observed in these reactions is consistent with an octahedral metal geometry that enforces predictable Zimmerman-Traxler transition structures. Moreover, the ligand composition of these metal complexes can be modulated to reverse the stereoselectivity of the aldol reaction, and presumably other reactions yet to be developed. Finally, the cost effectiveness of TiCl_4 when compared to other metal sources for soft enolization make it an ideal choice for many applications.

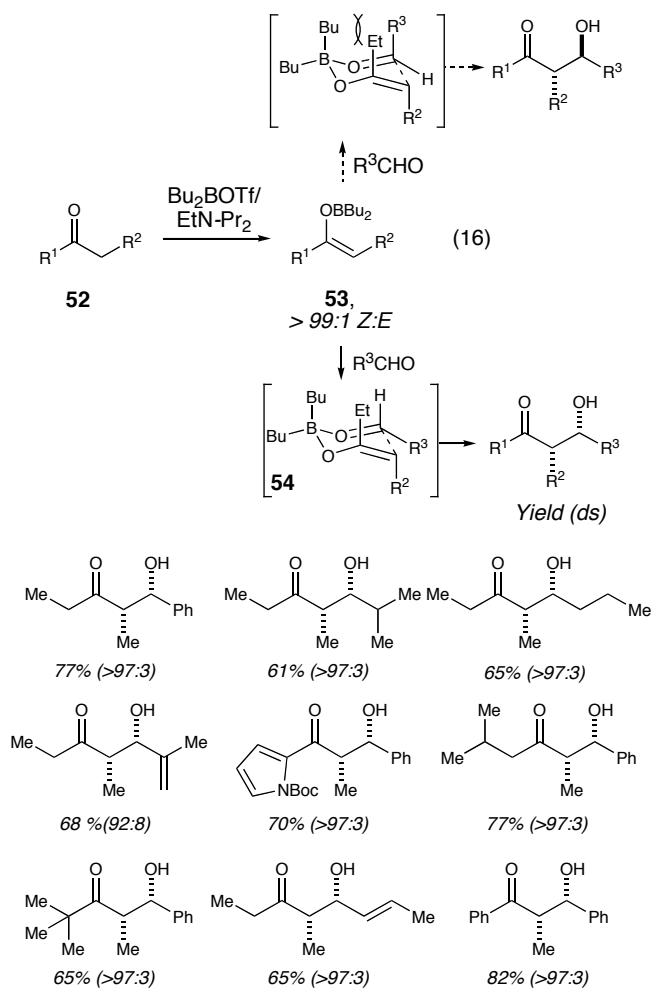
II. Boron

The most generally employed soft enolization technique involves the generation of boron enolates from dialkyl boron reagents. The reaction was first observed by Mukaiyama who employed dibutylboron triflate (Bu_2BOTf) and EtNi-Pr_2 for the soft enolization of ketones (eq 10).²⁵ The reaction was noted to be regioselective, but the diastereoselectivity was not evaluated. Furthermore, the intermediacy of the boron enolate was hypothesized, though no physical data to support the hypothesis was provided. Nonetheless, Mukaiyama's discovery led to the development of new aldol reactions that are broadly applicable to complex substrates.

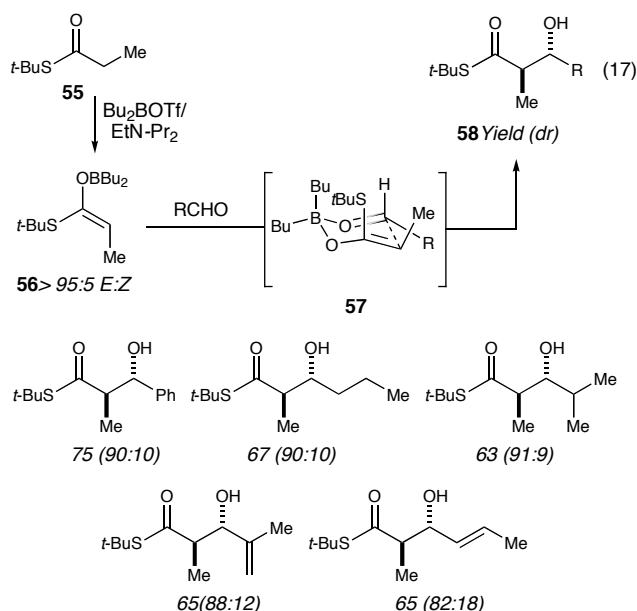


A detailed study from our group demonstrated that the boron aldol reaction was diastereoselective and the observed selectivity was linked to the geometry of the intermediate enolates (eq 16).²⁶

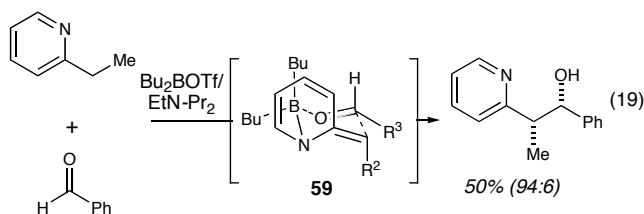
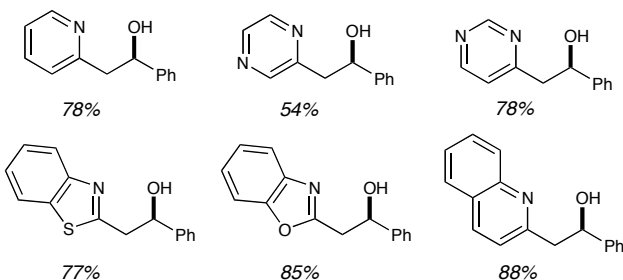
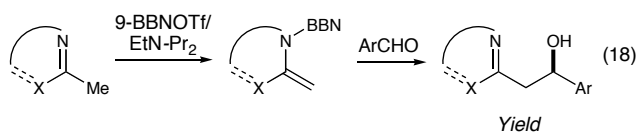
Treatment of 3-pentanone with Bu_2BOTf and EtNi-Pr_2 produced an enolate of >99:1 geometric purity for *Z*-isomer **70**. Subsequent treatment of this enolate with an aldehyde produced the corresponding aldol product **74** with >97:3 syn selectivity. The high syn selectivity is attributed to Zimmerman-Traxler transition state **73** in which diaxial steric interactions between enolate and aldehyde are minimized.²⁷



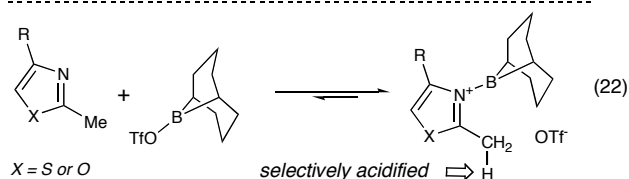
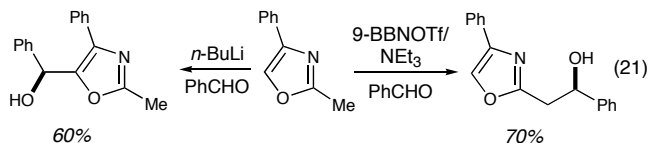
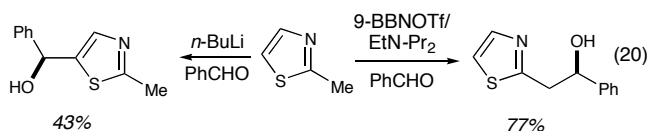
Nearly all of the ketones studied provided (*Z*)-enolates, but the selective formation of the (*E*)-enolate of *t*-butylthiopropionate demonstrated the expected turnover in selectivity to predominantly anti aldol product **58** (eq 17). Under the same conditions that were employed for ketones, enolization of *tert*-butyl thiopropionate **55** produced (*E*)-enolate **56** in >95:5 selectivity. When enolate **57** was allowed to react with aldehydes, the resultant aldol products **58** were formed with high anti selectivity as a result of chair transition state **57**.



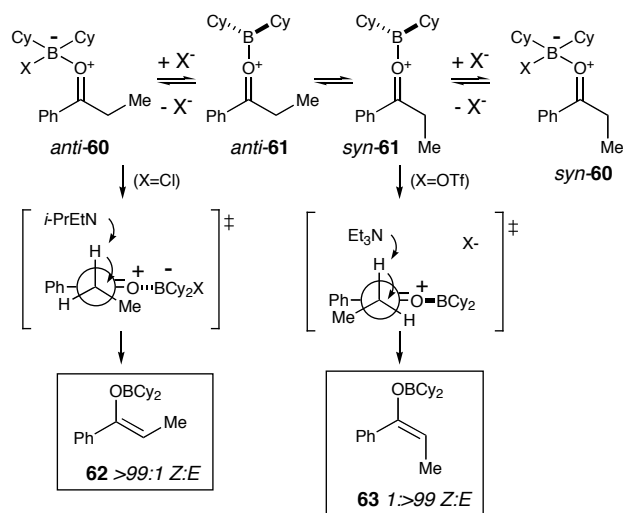
Soft enolization with boron has been generally limited to carbonyl compounds, but formation of imino-enolates of aromatic heterocycles has been observed (eq 18).²⁸ Higher temperatures and longer reaction times are necessary due to the reduced acidity of the exocyclic protons. The reaction works well for substituted pyridines and aromatic aldehydes, though electron rich aldehydes show reduced yield. Other heterocycles such as oxazoles and thiazoles also work well. In one case, ethylpyridine was shown to undergo a diastereoselective aldol-type reaction with syn selectivity that is consistent with chair transition state **84** (eq 19).²⁹



Soft “enolization” of substituted oxazoles and thiazoles displays completely complimentary chemoselectivity when compared to metallation with *n*-BuLi (eqs 20 and 21). When 9-BBNOTf and a trialkylamine base are employed, selective reaction at the methyl center is observed.³⁰ Alternatively, the use of *n*-BuLi produces exclusively metallation and reaction at the 5-position of the heterocycle. The origin of this chemoselectivity is not mentioned by Hamana, but it is probably due to the increased acidification of the exocyclic methyl group relative to the 5-position when the 9-BBNOTf binds to nitrogen (22).



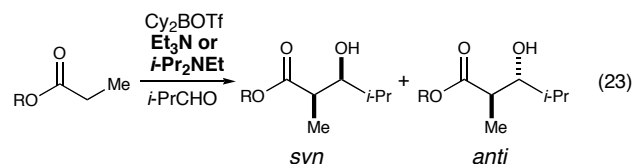
A general method for generating selectivity (*Z*)- or (*E*)-enolates from ketones by switching the boron reagent did not emerge until nearly ten years after the seminal study from the Evans group. Brown showed that by modulating the base, leaving group and substituents on boron, the enolization selectivity could be completely reversed (Scheme 6).³¹ A completely (*Z*)-selective enolization is achieved by using dicyclohexyl boron triflate and EtNi-Pr₂. Alternatively, the use of dicyclohexyl boron chloride and Et₃N produces predominantly the (*E*)-enolate. A simple rationalization lies in the fact that the triflate is completely displaced by the carbonyl oxygen, which alleviates a steric interaction between ketone substituent and the alkyl groups on boron. The approach of the incoming base in transition state **61b** forces the methyl group into a conformation that favors formation of enolate **62** with high *Z*-selectivity. In the case of dicyclohexyl boron chloride, an "ate" complex is formed, which causes increase steric crowding at the carbonyl oxygen. The methyl group is forced away and into a conformation leading to enolate **63** with high *E*-selectivity when the smaller base (Et₃N) approaches for enolization in the transition state.



Scheme 6. Selective formation of either *Z* or *E* enolates of propiophenone.

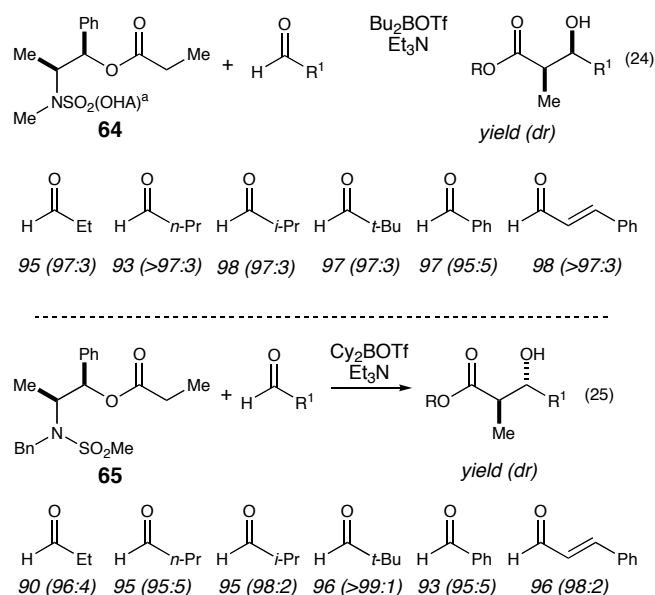
Enolization of esters with dialkylboron triflates was recently shown to lead to efficient aldol processes (eq 23).³² Ester substrates were previously overlooked due to their reduced acidity relative to ketones, thioesters, and imides. Abiko and Masamune

noted that the ensuing aldol reaction was generally syn selective and the selectivity was sensitive to the steric influence of the ester substituent. A switch to anti selectivity was observed with Cy₂BOTf was used in conjunction with Et₃N and benzyl or isopropyl propionate.



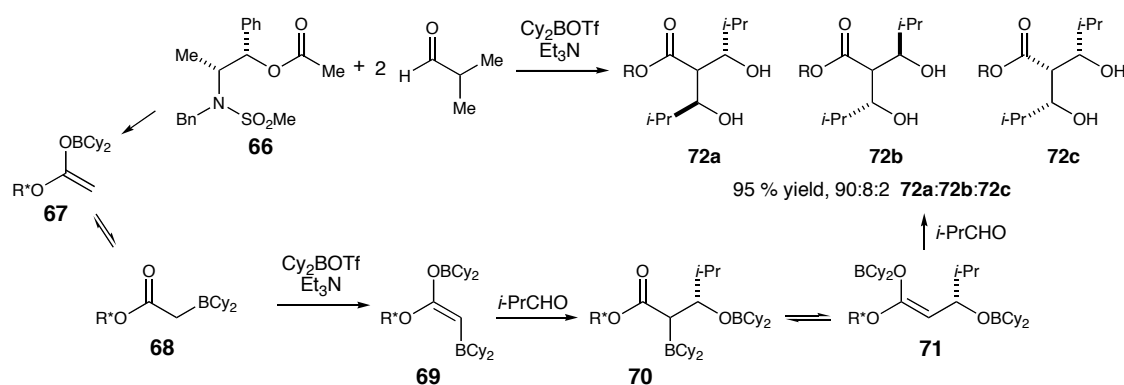
Et ₃ N		<i>i</i> -Pr ₂ NEt	
R	dr (syn:anti)	R	dr (syn:anti)
Me	95:5	Me	>95:5
Et	>95:5	Et	60:40
CH ₂ Cy	>95:5	CH ₂ Cy	70:30
<i>i</i> -Pr	85:15	<i>i</i> -Pr	30:70
Bn	90:10	Bn	10:90

Abiko later described two closely related chiral ester auxiliaries that provide access to syn and anti aldol products.³³ Ester **64**, derived from ephedrine exhibits high syn diastereoselectivity (>98:2) as well as a high level of discrimination between the diastereotopic faces of the chiral enolate (eq 24). Conversely, ester **65**, derived from norephedrine possesses a much smaller sulfonamide *S*-substituent and a larger *N*-substituent (eq 25). The differential ester substituents paired with the use of Cy₂BOTf in place of Bu₂BOTf result in a turnover to high syn selectivity, again with high stereoinduction from the auxiliary. While there are many selective syn aldol reactions, Abiko and Masamune's anti-aldol process is notable given the low number of anti-selective aldol reactions.



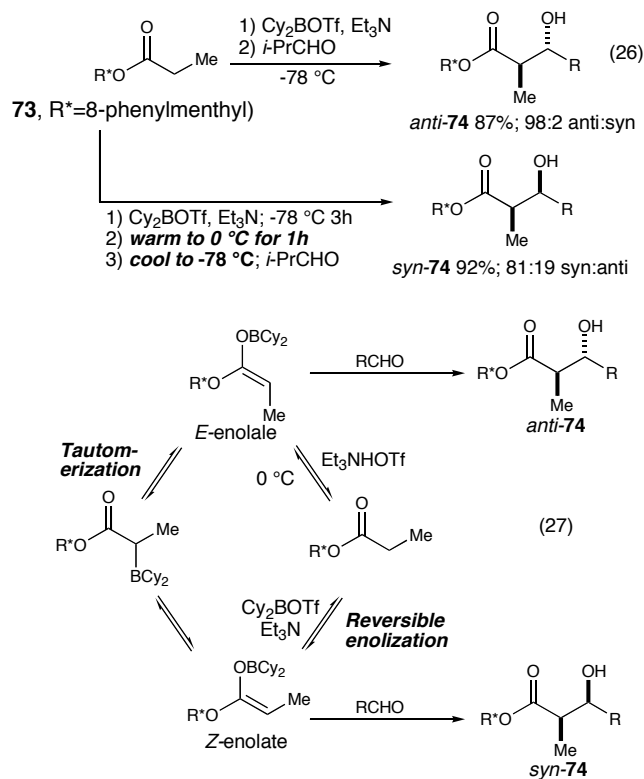
Scheme 7: Abiko's asymmetric ester aldol reactions. ^aOHA = 1,2,3,4,6,7,8,9-octahydroanthracenyl. ^b>98:2 syn:anti selectivity observed in all cases; dr refers to the ratio of syn diastereomers. ^c>95:5 anti:syn selectivity observed in all cases; dr refers to the ratio of anti diastereomers.

During the course of his studies on the generation of boron enolates from esters, Abiko observed an interesting double-enolization process (scheme 8).³⁴ When an acetate ester **66** was treated with Cy_2BOTf (2.5 equiv) and Et_3N (3.0 equiv) double addition product **72a** was observed along with minor diastereomers **72b** and **72c**.³⁵ A subsequent NMR study revealed the intermediacy of α -boryl enolate **69**.³⁶ This species is postulated to result from tautomerization of initially formed enolate **67** to the α -boryl keto form **68**, which undergoes enolization by the excess Cy_2BOTf and Et_3N which are present.³⁷ When treated with an aldehyde, α -boryl enolate **69** forms α -boryl aldolate **70**, which tautomerizes to β -hydroxy enolate **71** before reacting with another equivalent of aldehyde to form "double" aldol products **72a-c**.

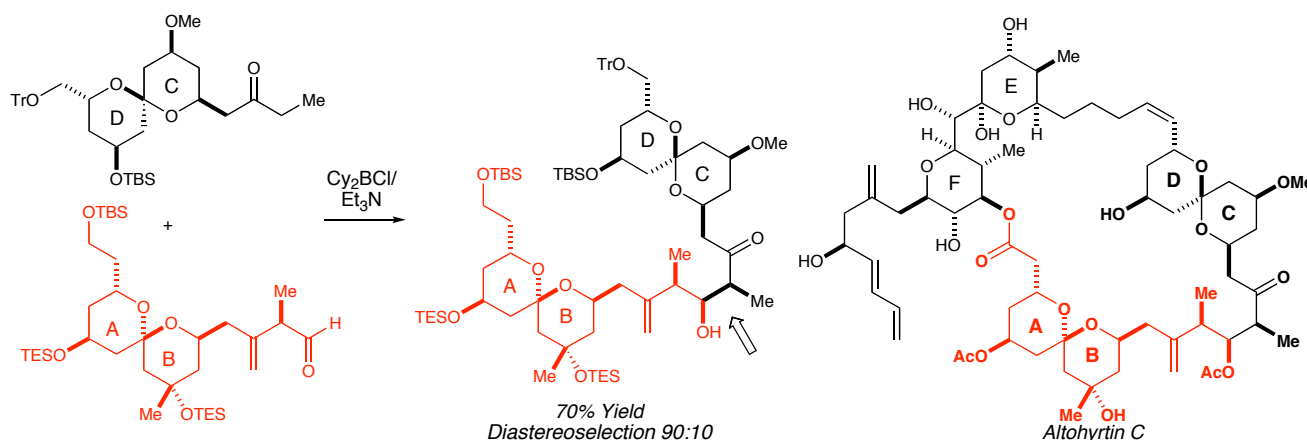


Scheme 8: Mechanism of Abiko's double aldol reaction.

In marked contrast to their thioester, ketone and imide counterparts, boron enolates of esters were found to undergo E/Z isomerization if left standing at 0°C. Ester **106** reacts with isobutyraldehyde at -78 °C under the standard conditions to produce the *anti*-**107** with high selectivity. If the reaction mixture is warmed to 0 °C for 1h, then re-cooled to -78 °C before adding the aldehyde, *syn*-**107** is formed as the major product. Abiko and Masamune speculate that this observation stems from reversible enolization at the higher temperature. Based on later observations reported by Abiko in the double aldol reactions (*vide supra*), tautomerization of boron enolate (*E*)-**108** would also explain the E/Z isomerization.



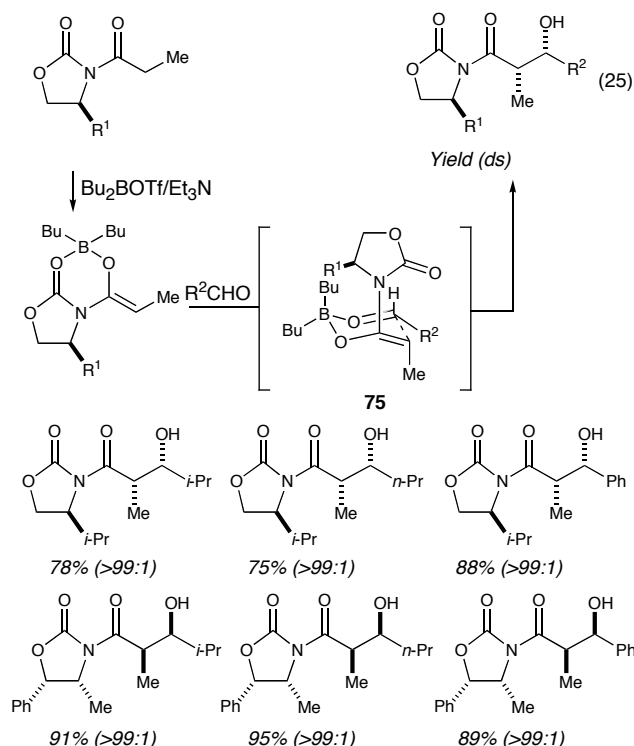
The generation of boron enolates through soft enolization occurs under such mild conditions that it is the aldol process that is the most amenable to the coupling of highly complex substrates (Scheme 7). The aldol reaction is a particularly attractive reaction for late-stage fragment coupling, since both components of the reaction can be recovered in the event that the reaction does not proceed to completion. This property sets the boron aldol apart from most cross coupling reaction in which a carbanion precursor is reduced in the process making recovery of unreacted material impossible. Finally, given the low Lewis acidity of Bu_2BOTf , the reaction is tolerant of functionality that would not survive other metals used for soft enolization. The highly diastereoselective aldol coupling step *en route* to Altohyrtin C demonstrates the regio-, diastereo-, and chemoselectivity that one can achieve in the boron aldol reaction (scheme 9).³⁸



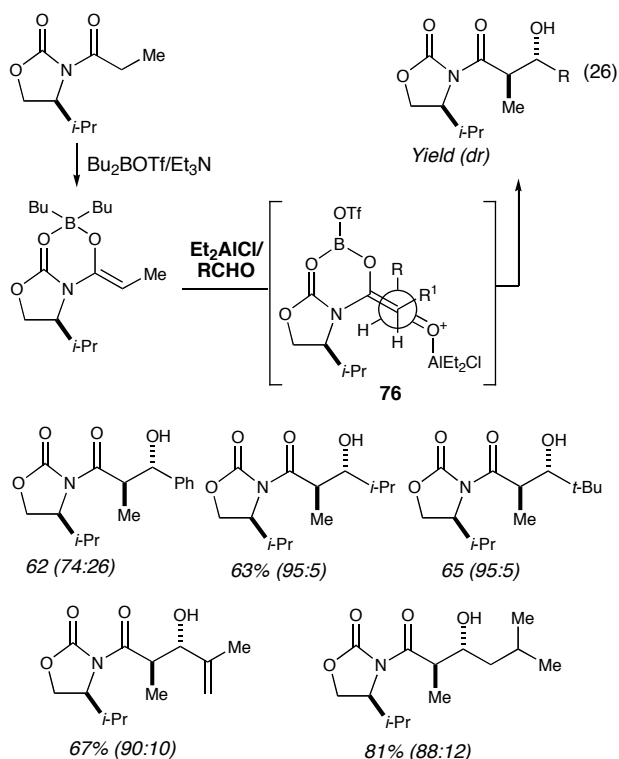
Scheme 9. Complex fragment coupling using soft enolization with boron: Synthesis of altohyrtin C

The first general and widely utilized asymmetric aldol reaction employed boron enolates produced by the soft enolization of *N*-acyl oxazolidinones (eq 17).³⁹ The reaction shows excellent syn selectivity resulting from transition state **116** whereby the imide carbonyl is dissociated to accommodate the aldehyde carbonyl in a cyclic transition state. The wide tolerance of this reaction to aldehyde structure and enolate substitution has resulted in the synthesis of a myriad of natural products and medicinal compounds. One limitation is the lack of selectivity observed in the reactions

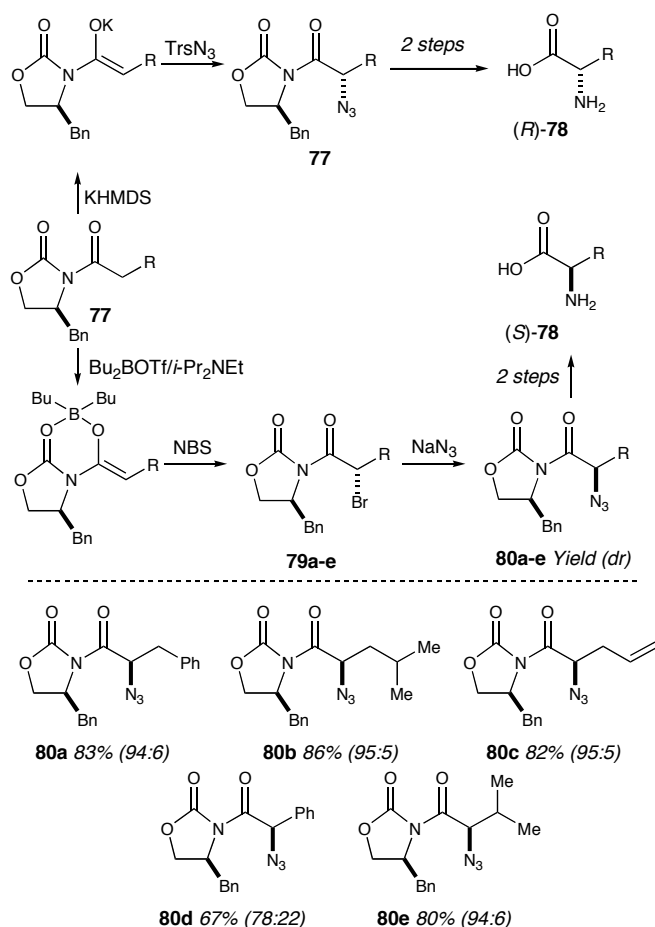
of acetate-derived enolates, though this shortcoming has been alleviated by the use of other auxiliaries and metals.



While the selectivity of the boron aldol reaction is typically syn, Heathcock discovered a set of conditions in which the selectivity can be reversed to anti (eq 26).⁴⁰ It was found that precomplexation of a Lewis acid to the aldehyde acceptor prevents the normal cyclic transition state and forces an acyclic array leading to the anti product. The proposed transition state is consistent with the one proposed by Nagao to explain the results of his *N*-acyliminium ion reaction with a Sn(II) enolate in which a similar diastereochemical outcome is observed (*vide infra*). The initial discovery was made when excess dibutylboron triflate was used, in which case the first equivalent facilitates enolate formation and the second equivalent complexes the aldehyde. A comparative study later showed that Et₂AlCl was the most anti-selective Lewis acid and showed modest to high selectivity for a series of aldehydes. Transition state **120** is most favored when bulky Lewis Acids are employed and the anti-periplanar configuration likely arises from minimization of the dipole-dipole interactions of the aldehyde and enolate.

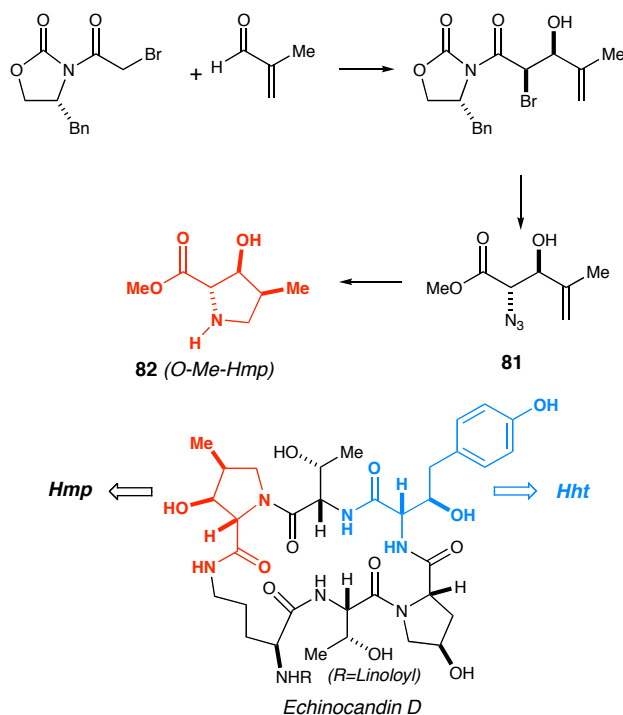


Boron enolates do not undergo acylation, alkylation, or most group-transfer reactions, but they are useful for diastereoselective halogenation, the products of which can be converted to synthetically useful azides.⁴¹ (*R*)- α -Azido imides **77** are generated directly by the action of 1,3,5-triisopropyl benzenesulfonamide (TrsN_3) on the corresponding potassium enolates generated with KHMDS (Scheme 10).⁴² The complimentary (*S*) diastereomers **81a-e** leading to the enantiomeric amino acids, are available from the same antipode of auxiliary through halide displacement. The requisite halides are most easily made through treatment of the boron enolates with *N*-bromosuccinimide.⁴³ Thus, both enantiomers of amino acid (*R*)- and (*S*)-**125a-e** are available from the same isomer of auxiliary **122a-e**.



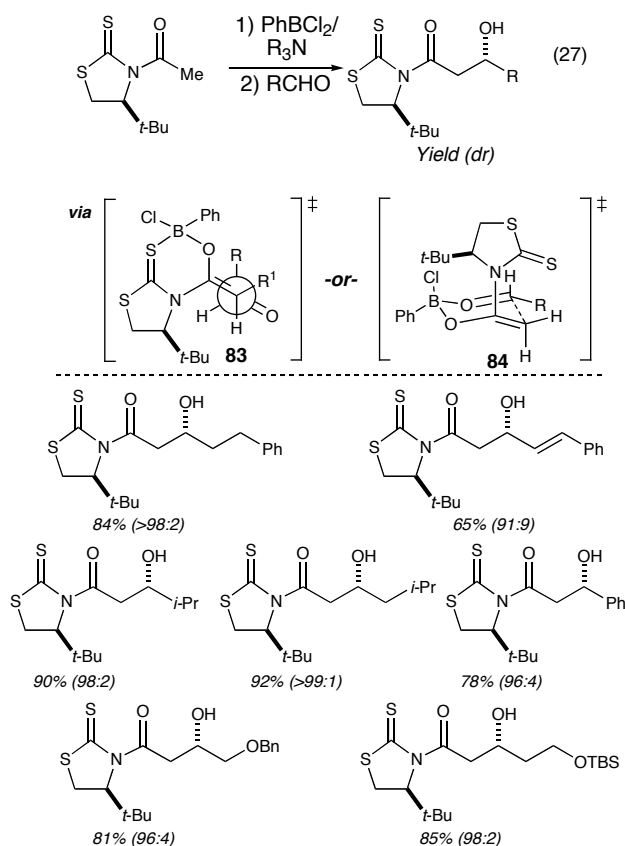
Scheme 10. Diastereoselective synthesis of enantiomeric α -amino acids.

A related α -amino acid synthesis proceeds by the diastereoselective aldol reactions of bromoacetyl oxazolidinones via their boron enolates (Scheme 11). This method was applied to the synthesis of the Hmp residue of echinocandin D.⁴⁴ In this case, a serendipitous discovery allowed for the direct conversion of azido-aldol **81** to the requisite 3-hydroxy-4-methyl proline precursor **82**. The requisite syn β -hydroxy α -amino acid residue (Hht) of echinocandin D was formed via an Sn(II)-mediated aldol reaction (*vide infra*).

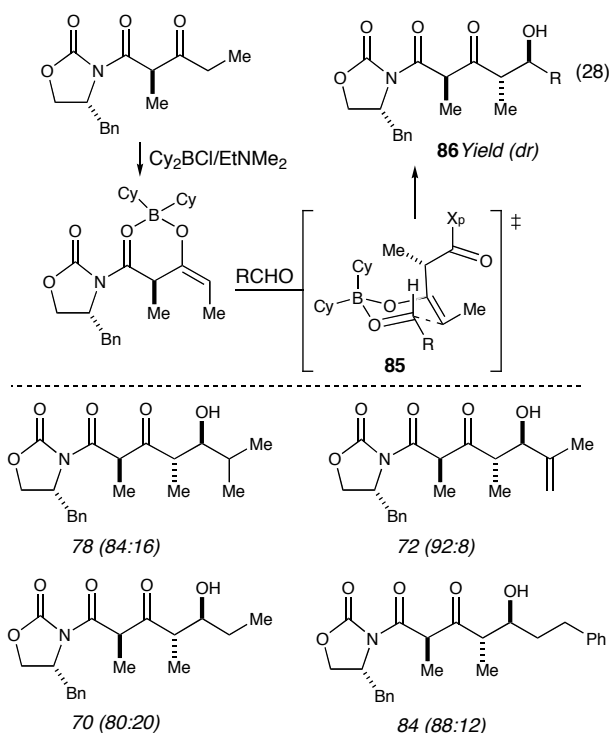


Scheme 11: Preparation of a non-natural α -amino acid applied to the synthesis of echinocandin D

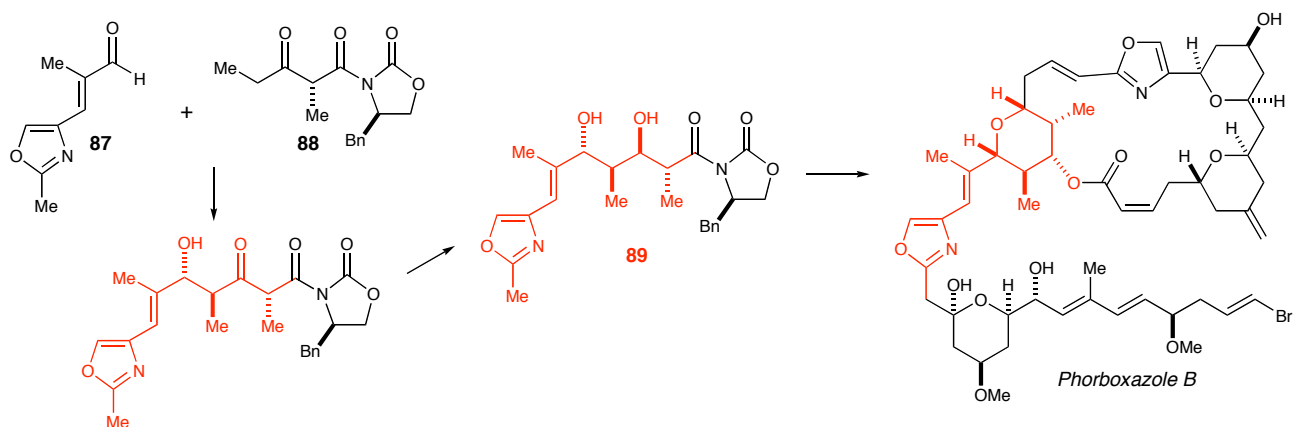
Selective acetate aldol reactions are possible when a thiazolidinethione auxiliary is combined with phenylboron dichloride. Samakia has shown that this reagent combination results in very high selectivities for the aldol reaction, and that the substrate scope is excellent (eq). Related reactions have been reported for titanium (*vide supra*) and tin (*vide infra*).



Like titanium, boron activation of β -keto imides allows for selective formation of propionyl enolates and fortuitously their reaction with aldehydes produces a complimentary diastereomer (eq 19).⁴⁵ Instead of the all syn isomer (Scheme 4, *vide supra*), the boron enolate produces the 1,4-syn diastereomer **86**. The enolization conditions likely produce the (*E*)-enolate which reacts through chair-like transition state **85**, producing the anti aldol product. The sense of absolute induction results from minimizing the interaction of the methyl group with the cyclohexyl groups on boron.



This β -keto imide aldol reaction via the boron enolate has served as a key component to the preparation of several anti-propionate natural products. The polypropionate region of phorboxazole B was prepared in a short sequence beginning with the aldol reaction between **87** and **88**, followed by directed anti reduction to produce **89** (Scheme 10).⁴⁶ The resultant stereotetrad was subsequently cyclized and used to form one of the tetrahydropyran rings of phorboxazole B.

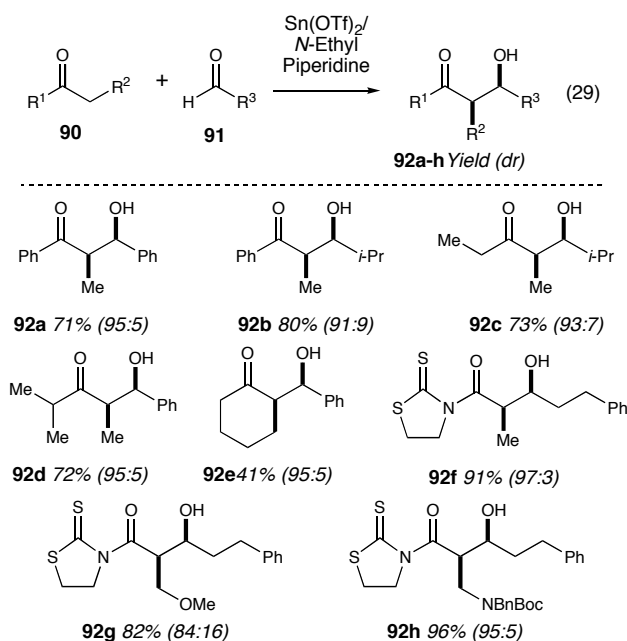


Scheme 12. The boron β -keto imide aldol reaction in the synthesis of phorboxazole B.

Boron enolates generated through soft enolization exhibit the best balance of substrate tolerance and mild generation. Though limited almost exclusively to aldol reactions, boron enolates show exquisite diastereoselectivity that has been applied to highly complex and sensitive substrates. Proper choice of reaction conditions for ketones can favor either (*E*)- or (*Z*)- enolates and thus almost exclusively the syn or anti aldol products, respectively. The necessary boron halides and triflates are readily available from easily handled precursors and the reaction has been executed on large scale.

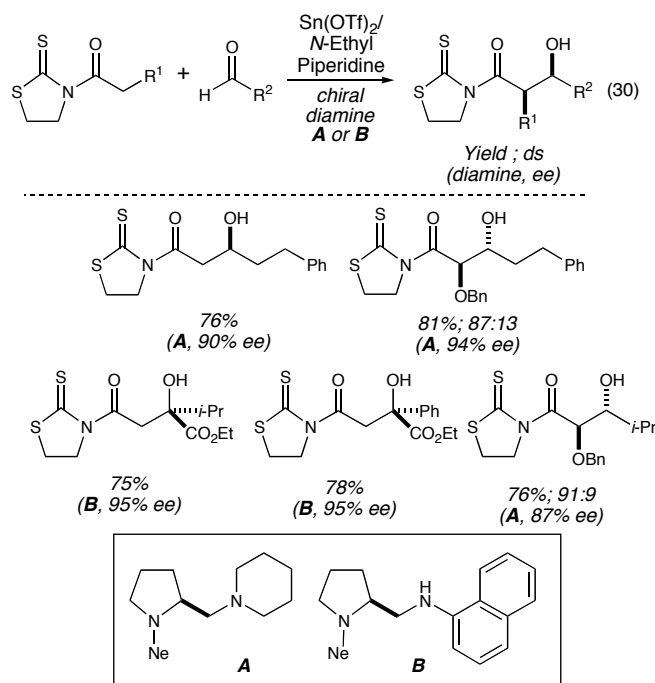
III. Tin (II)

In 1982, Mukaiyama introduced a new soft enolization procedure employing $\text{Sn}(\text{OTf})_2$ and a trialkylamine base (eq 29).⁴⁷ The method was used initially for ketone derived enolates. The conditions are so mild that only very acidic substrates are suitable, so Mukaiyama later introduced the thiazolidinethione as an ester surrogate.⁴⁸ Ketones and thiazolidinethiones both reacted with high diastereoselectivity and yield. The soft nature of the $\text{Sn}(\text{II})$ enolate even allows effective enolization of substrates possessing β -heteroatoms, such as **92g** and **92h**, that would eliminate under most other enolization conditions.⁴⁹

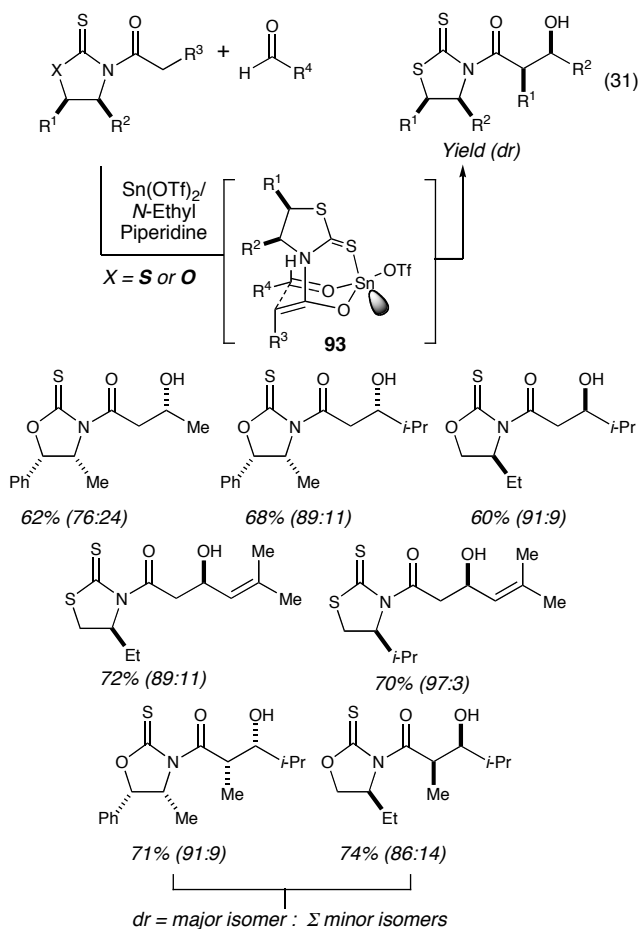


The $\text{Sn}(\text{OTf}_2)$ -mediated aldol was first made asymmetric by Mukaiyama by adding a chiral, chelating diamine ligand (eq 30).⁵⁰ The chiral

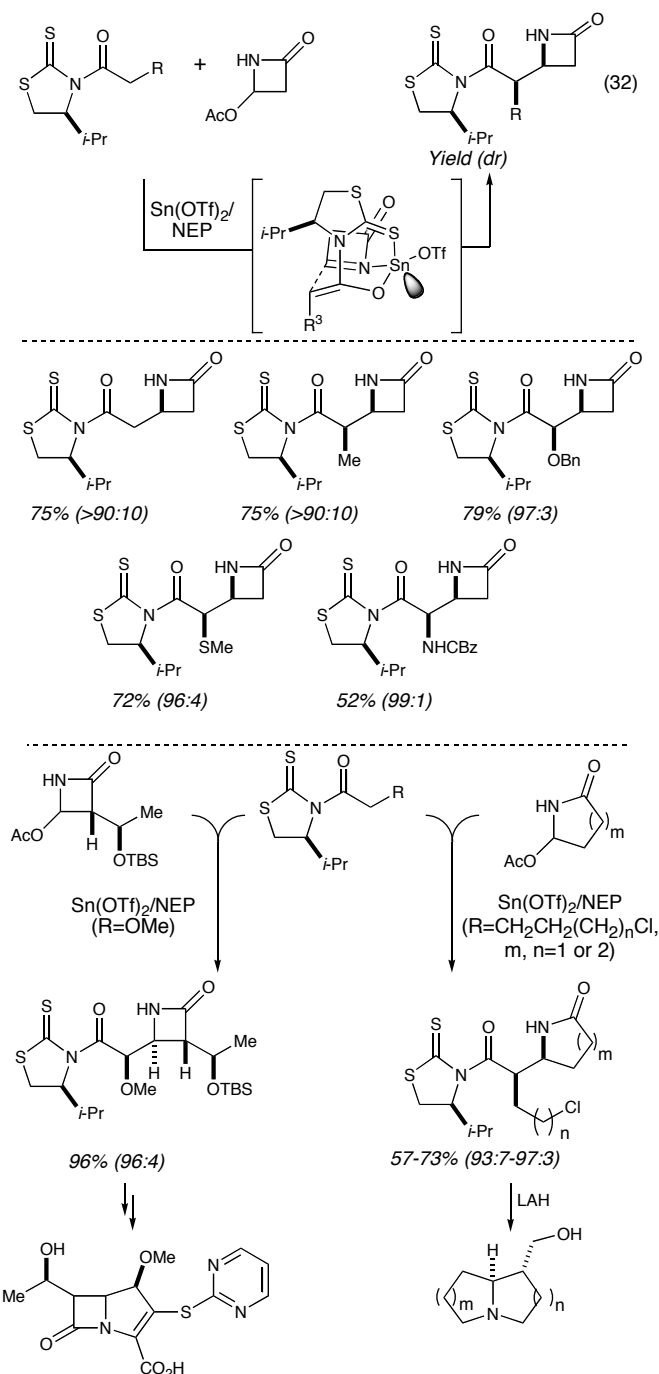
Sn(II) enolate complex confers very high selectivity to the subsequent aldol reaction. This method was employed for acetate and glycolate enolates which both exhibited high enantioselectivity and diastereoselectivity.



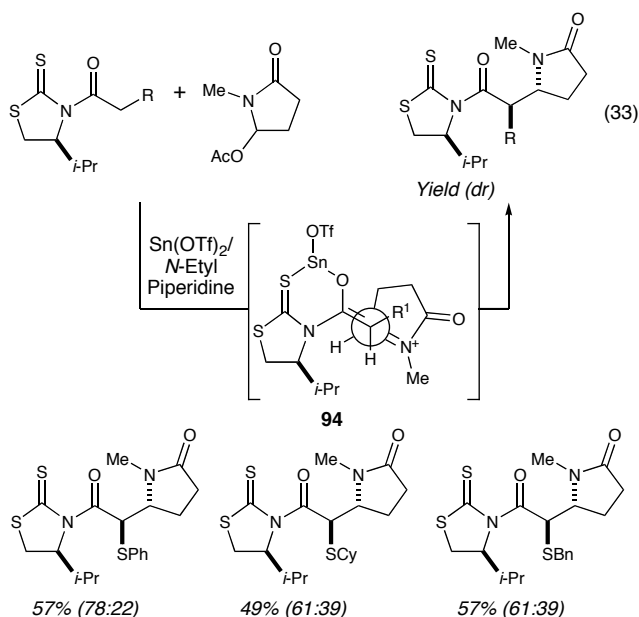
A subsequent asymmetric aldol reaction was developed which employed a chiral thiazolidinethione auxiliary (eq 31).⁵¹ Nagao demonstrated that the reaction was highly proficient for acetate aldol reactions.⁵² Previous to the observations of Andrews (*vide supra*), this was the first and only example of an efficient asymmetric acetate aldol reaction. While Nagao mentions that the reaction works well for propionate substrates, this reaction was only recently reported in the form of preparative reactions employed by Kocienski,⁵³ Rizzacasa,⁵⁴ and Paquette.⁵⁵



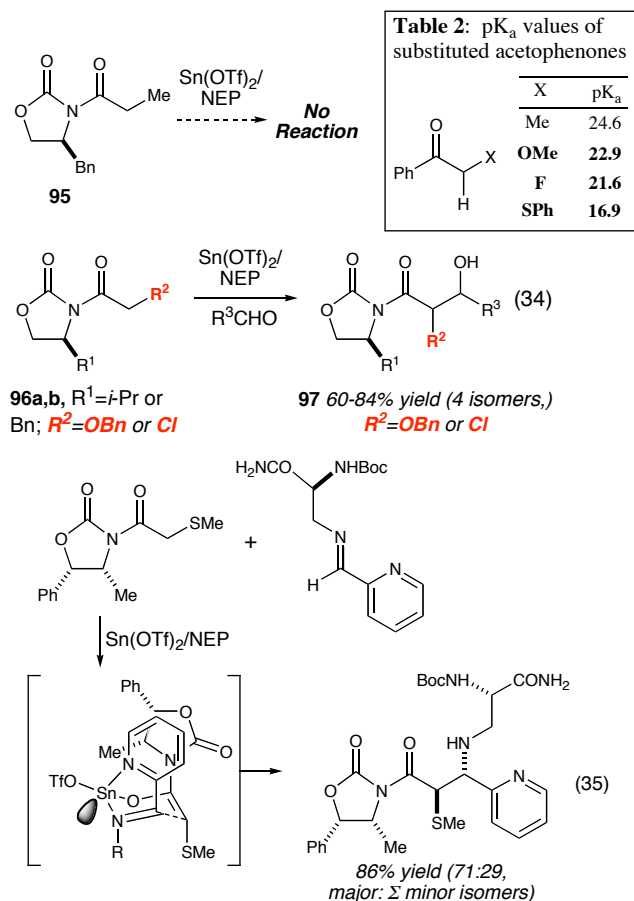
The reduced Lewis acidity of $\text{Sn}(\text{II})$ enolates, relative to those derived from boron and titanium, allows these nucleophiles to perform well in Mannich-type reactions with imines (eq 32). Nagao has observed high selectivity in the addition of $\text{Sn}(\text{II})$ enolates of thiazolidinethiones to cyclic imine precursors. The sense of diastereoselection is consistent with a cyclic transition state analogous to that of the aldol reaction. This reaction has proven useful in the preparation of non-natural carbapenem antibiotics⁵⁶ and bicyclic alkaloids⁵⁷ (eq 24).



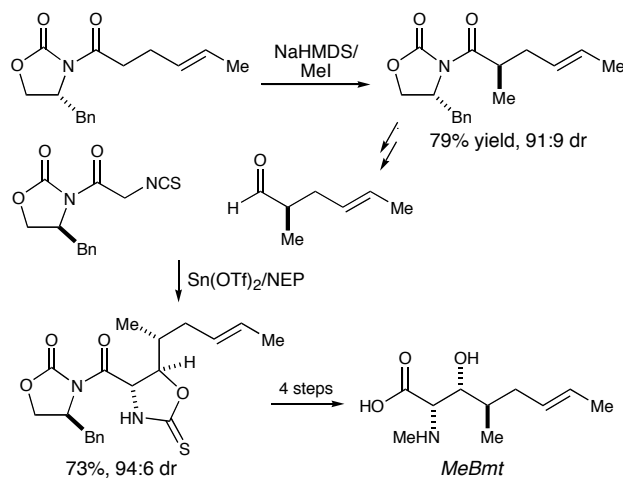
Nagao noted an interesting stereochemical reversal in his studies of the imine addition reactions (eq 33).⁵⁸ When *N*-methyl lactam precursors were employed, the anti diastereomer predominated. Since the precursor forms an *N*-acyl iminium ion upon elimination of acetic acid, rather than a neutral imine, open transition state **94** is favored which leads to the anti diastereoselection. This observation is consistent with those of Urpí and Heathcock (*vide supra*) where open transition states were observed for titanium and boron enolates, respectively.



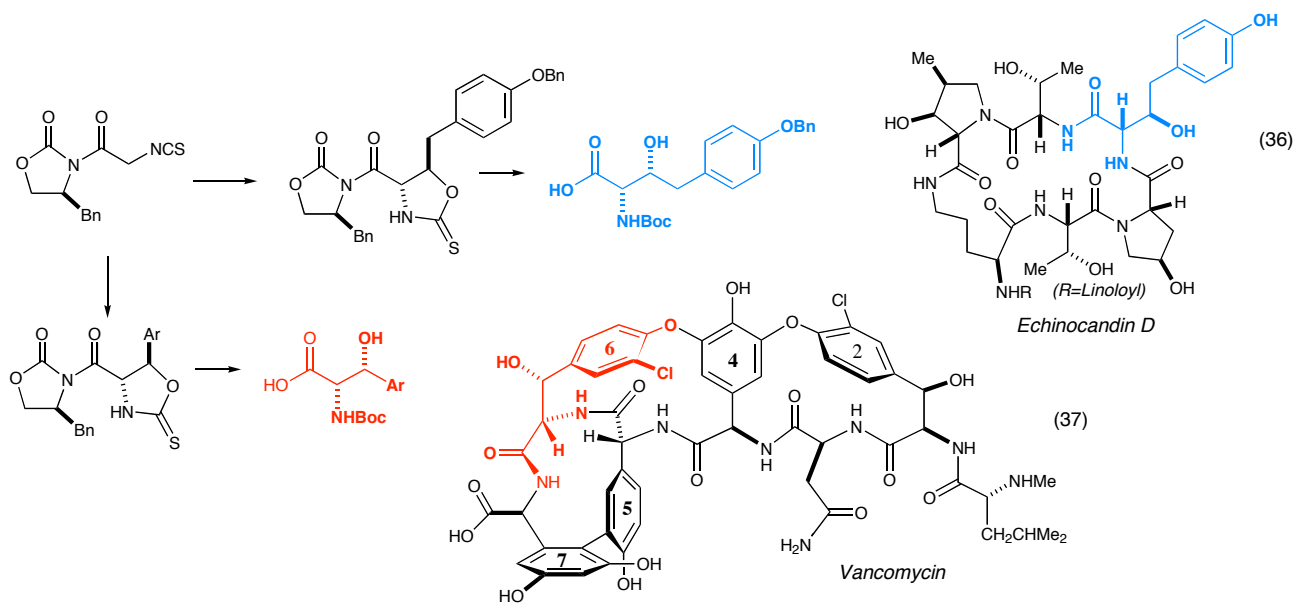
While most reactions of $\text{Sn}(\text{II})$ enolates have employed thiazolidinethiones, there are cases in which an oxazolidinone is suitable. The combination of $\text{Sn}(\text{OTf})_2$ and a trialkylamine base results in little or no enolization of propionyl oxazolidinone (eq 27). The substitution of the methyl group for an inductively electron-withdrawing substituent is sufficiently activating to allow enolization, consistent with the known pK_a values for substituted acetophenones (table 2). Our group explored the $\text{Sn}(\text{II})$ -mediated aldol reaction of glycolate-derived oxazolidinone **96a** ($R^2=\text{OBn}$) in the total synthesis of Calyculin (eq 34).⁵⁹ Pridgen showed that α -chloroacetyl oxazolidinones **96b** ($R^2=\text{Cl}$) readily enolize and produce the corresponding aldol products in low diastereoselectivity (eq 34).⁶⁰ Boger observed modest diastereoselectivity in his Mannich reaction en route to bleomycin analogs (eq 35).⁶¹ In that case, the thiomethylacetyl oxazolidinone serves as an acetyl synthon and provides the necessary β -amino acid in high yield.



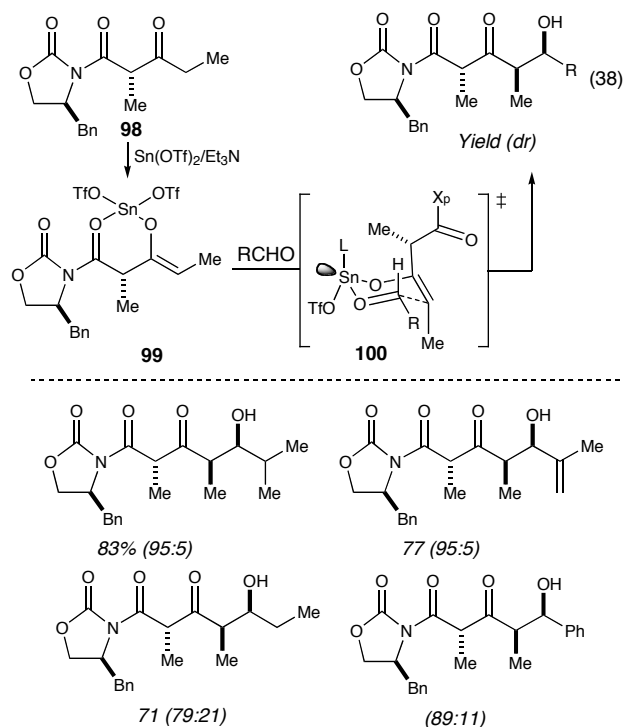
Our group discovered that Sn(II) enolates were uniquely qualified for the preparation of β -hydroxy- α -amino acids (Scheme 11).⁶² α -Thiocyanato oxazolidinones react smoothly to give diastereomerically pure oxazolidinone aldol products. This method was first reported in our synthesis of cyclosporin's unusual amino acid MeBmt and later applied to syntheses of amino acid residues found in echinocandin D²⁸ and vancomycin (eqs 36 and 37).⁶³



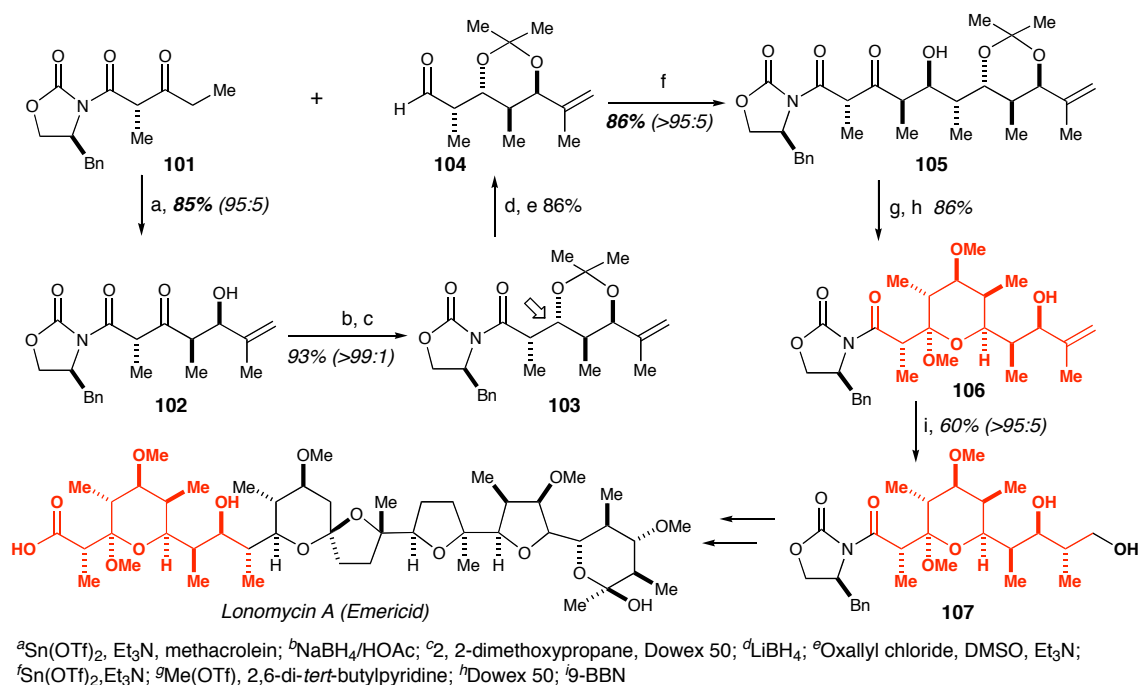
Scheme 11. The Sn(II) aldol reaction applied to the synthesis of the MeBmt residue of Cyclosporin.



The use of $\text{Sn}(\text{OTf})_2$ in the β -keto imide aldol proved fruitful in that a different diastereomer is produced when compared to boron and titanium.¹⁴ When treated with $\text{Sn}(\text{OTf})_2$ and triethylamine, β -keto imide **98** formed exclusively (*Z*)-enolate **99**. The ensuing aldol reaction likely proceeds through transition state **100**, similar to that of the boron mediated process, but with the expected syn stereochemical outcome (eq 33).



The $\text{Sn}(\text{OTf})_2$ -mediated β -keto imide aldol process was particularly well-suited to the rapid assembly of the polyketide natural product lonomycin A (emericid).⁶⁴ The $\text{Sn}(\text{II})$ enolate of β -keto imide **101** was treated with methacrolein, then cleaved to aldehyde **104** after reduction and protection as the acetonide. A second equivalent of $\text{Sn}(\text{II})$ enolate derived from imide **101** was added to aldehyde **104** in a double-diastereodifferentiating aldol reaction to producing ketone **105**. Deprotection, and concomitant cyclization, of ketone **105** produced methallyl alcohol **106**, which was diastereoselectively hydroborated to produce diol **107**, a key intermediate possessing 9 contiguous stereogenic centers of lonomycin A.



Scheme 12. Iterative β -keto imide aldol reactions in the synthesis of lonomycin A (emerid)

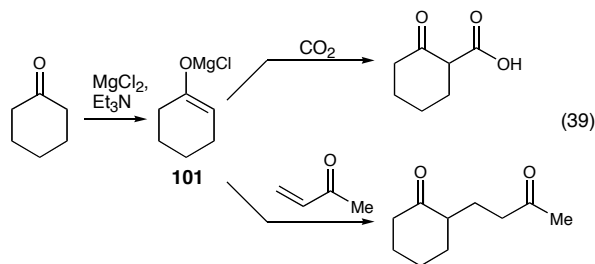
Enolization of carbonyl compounds with Sn(OTf)₂ and a trialkylamine base is the mildest method of enolate generation discussed in this review. Substrates are limited to acidic carbonyls such as ketones and thiazolidinethiones as well as a limited subclass of oxazolidinones. The low reactivity, however, allows for wide functional group compatibility and a unique tolerance of substrates that β -eliminate under all other enolization conditions. In addition, the reduced Lewis acidity of the Sn(II) center allows for their use in Mannich reactions. The mild conditions for generating Sn(II) enolates results in overall reduced reactivity of these enolates, which is simultaneously their biggest limitation and their best asset.

IV. Magnesium

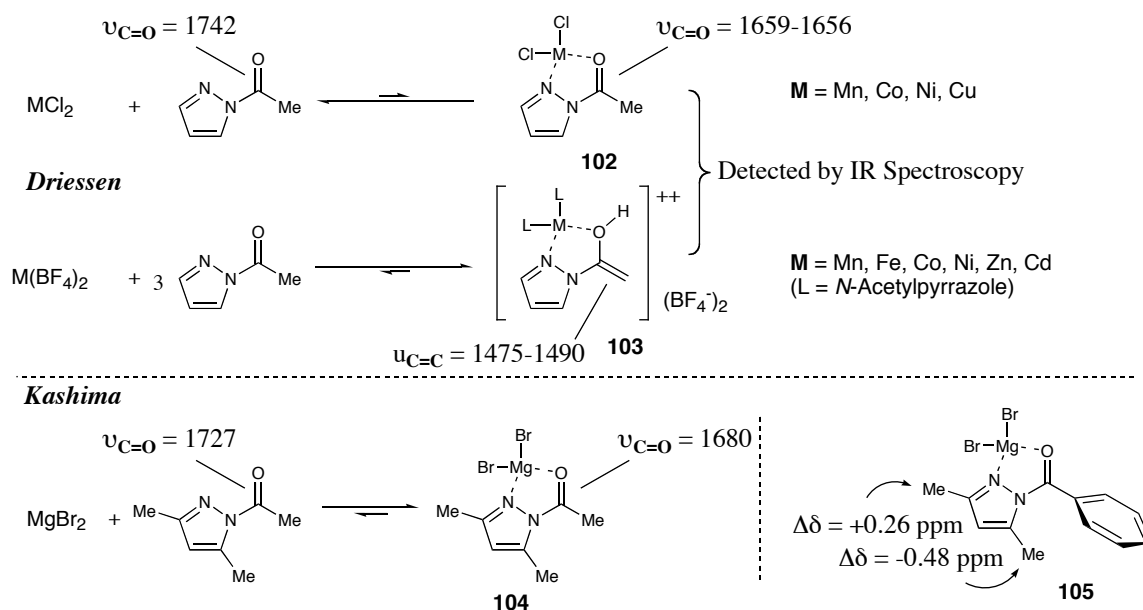
Recent advances in the enolate chemistry of magnesium halides demonstrate the increasingly important role that these nucleophiles will likely play in future reaction development. Unlike dibutylboron triflate, titanium tetrachloride, and stannous triflate, magnesium salts are extremely cost-effective and easy to handle. The gains in handling ability, however, are accompanied by losses in reactivity

such that soft enolization with magnesium is subject to limited substrate scope. Nonetheless, magnesium enolates have been developed in several useful reactions.

The first observation of a reaction that proceeds via the intermediacy of a magnesium enolate was made by Rathke.⁶⁵ Triethylamine and magnesium chloride were observed to facilitate enolate carboxylations and Michael reactions (eq 34). Rathke proposes that the reaction proceeds via magnesium enolate **101**.

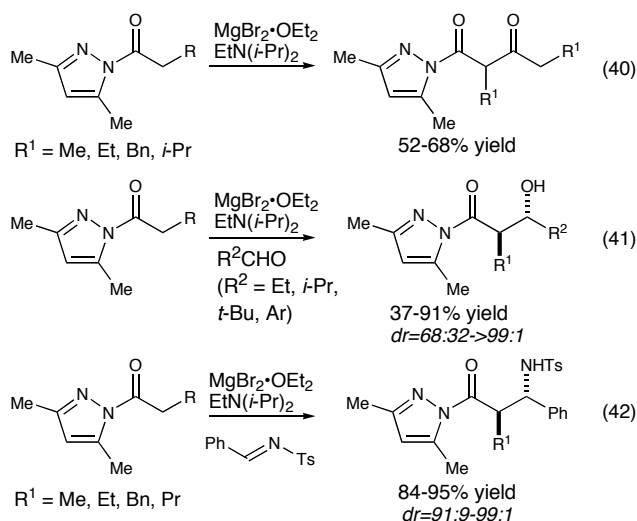


Kashima observed soft enolization with magnesium bromide in his investigations of acylpyrroles and was eventually the first to report an aldol reaction involving soft enolization with magnesium. Previous to Kashima's work, acylpyrroles had been identified as effective chelating ligand for divalent transition metals (scheme 12). Driessen demonstrated that various transition metals form 1:1 complexes **204** with transition metal chlorides in which a shift in the IR spectrum was consistent with binding of the metal ion to the carbonyl oxygen and pyrrole nitrogen.⁶⁶ Furthermore, it was shown that the complexes of metal tetrafluoroborates exhibited a shift toward the enol tautomer **205** due to the increased Lewis acidity of the metal centers. Kashima's results with magnesium suggest binding of magnesium bromide to the acylpyrrole to form complexes **207** and **208** with no shift toward the enol tautomer visible in either the IR or ^1H NMR spectra.

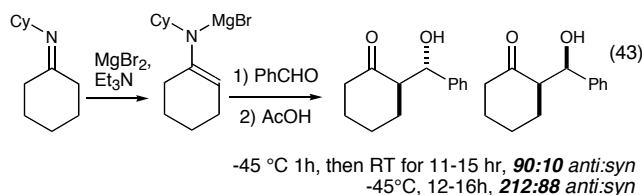


Scheme 12. Observation of magnesium chelation and enolization with acylpyrazoles.

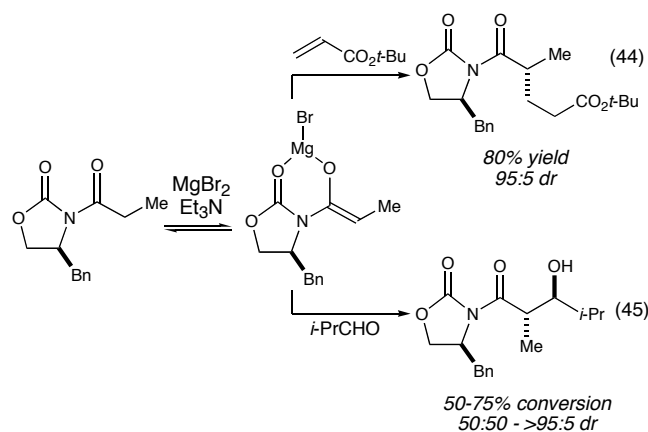
Acylpyrazoles undergo soft enolization and subsequent reaction *via* the resultant magnesium enolate. The addition of Hünig's base to pyrazoles **106** resulted in the formation of Claisen condensation products through acylation of the enolate by acylpyrazole (eq 35).⁶⁷ The reaction was most effective for substituted enolates. Based on this observation, Kashima later reported diastereoselective aldol⁶⁸ and Mannich⁶⁹ reactions (eqs 36 and 37). While each of these reactions showed modest to good anti diastereoselection, the use of chiral pyrazoles failed to induce useful levels of asymmetry.



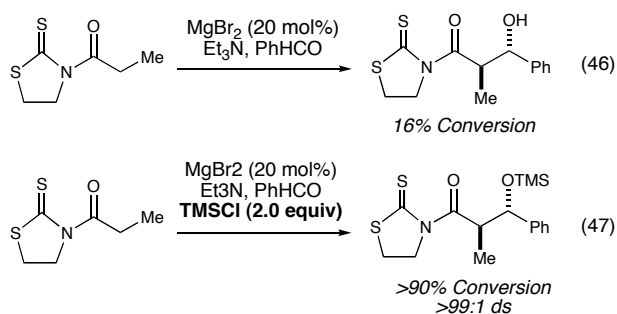
Nagao has reported the use of soft enolization for imino aldol reactions.⁷⁰ The cyclohexyl imine of cyclohexanone undergoes an aldol addition with treated with MgBr_2 and triethylamine (eq 43). The reaction is anti selective under kinetic control (low temperature), but at higher temperatures, the syn product predominates, indicating that the reaction becomes reversible at higher temperatures.



Early studies from our laboratories indicated that magnesium enolates might be good nucleophiles for selective reactions. The deuterium quench experiments (table 1, *vide supra*) indicated that magnesium bromide facilitated reversible enolization of propionyl oxazolidinone and that 25% of the enolate was present at equilibrium. In previously unpublished experiments, propionyl oxazolidinone **218** was shown to undergo a diastereoselective Michael reaction in good yield (39).⁷¹ While the selectivity and yield are both lower than those of the analogous experiment with titanium tetrachloride, this experiment indicated that partial enolization paired with an irreversible reaction could lead to high conversion. In a related study, it was shown that stoichiometric quantities of magnesium bromide would also facilitate the aldol reaction with variable selectivity and yield (eq 40). In the latter case, it is clear that the stability the magnesium aldolate is the driving force for the reaction.

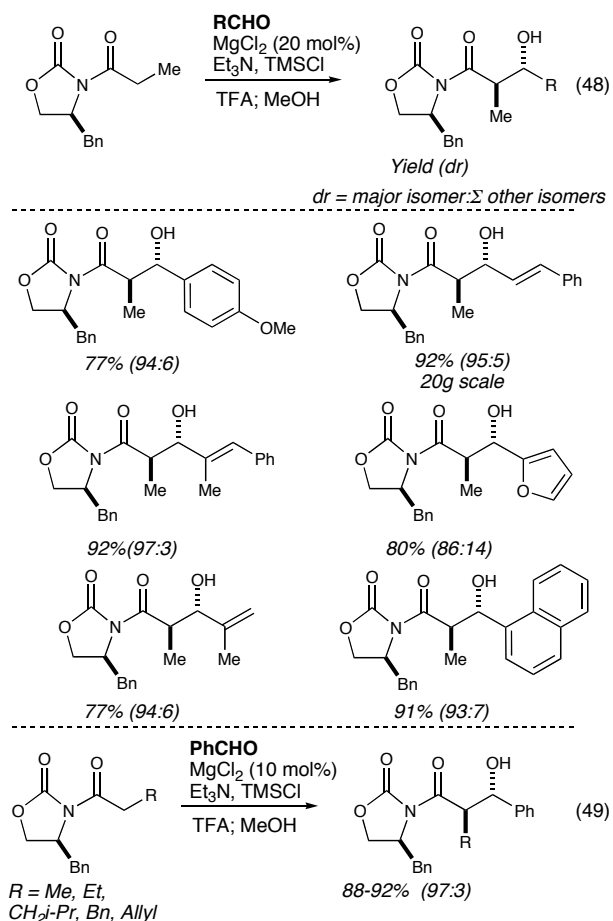


The reversible nature of soft enolization with magnesium led us to investigate the possibility of developing a catalytic aldol process. While the stoichiometric process gives modest conversion, we found that the use of a catalytic quantity of magnesium bromide did not yield a catalytic process, even when the more acidic acyl thiazolidinethione was employed (eq 46). Based on Fürstner's key insight into silylation as a turnover event in various chromium and titanium catalyzed processes,⁷² we explored the use of silylating agents to increase the conversion of the magnesium aldol reaction. Indeed, when the thiazolidinethione experiment was repeated in the presence of a stoichiometric quantity of chlorotrimethylsilane, high conversion and exceptional anti diastereoselectivity were observed (eq 47).



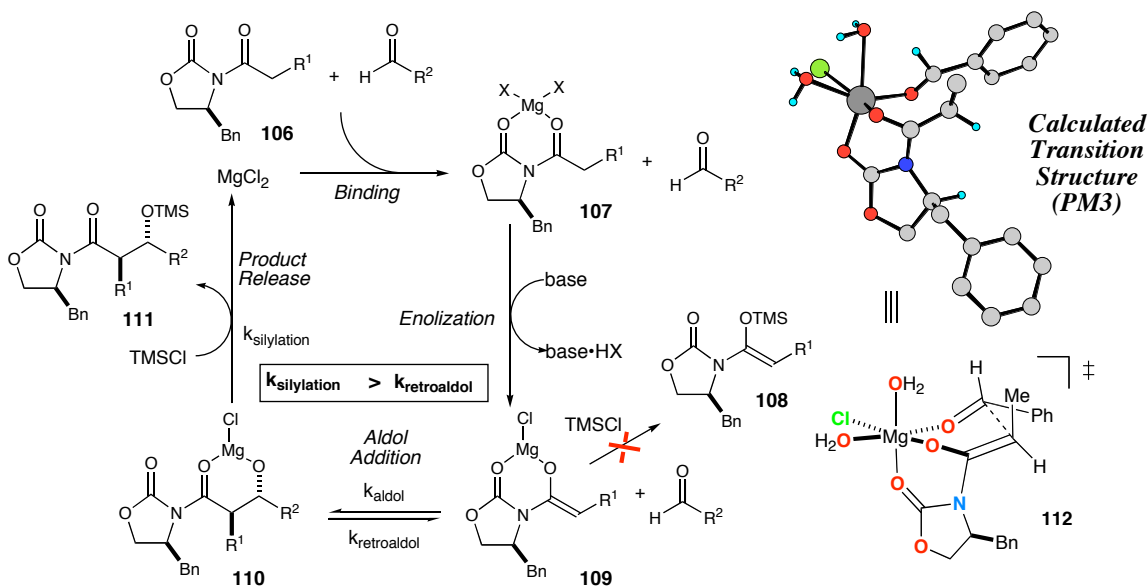
Our magnesium-catalyzed aldol process was found to exhibit exceptionally high asymmetric induction with the use of chiral acyl oxazolidinones.⁷³ The predominant isomer was formed preferentially to the other three possible isomers in 86:14 to 97:3 selectivity (eq 48). The aldol addition proceeds with anti diastereoselection, and

the relative configuration with respect to the auxiliary is analogous to the boron-mediated syn-selective aldol reaction. Non-enolizable aldehydes all exhibit high selectivity and yield. In addition, the reaction is tolerant to a variety of substituents on the acyl residue (eq 49).



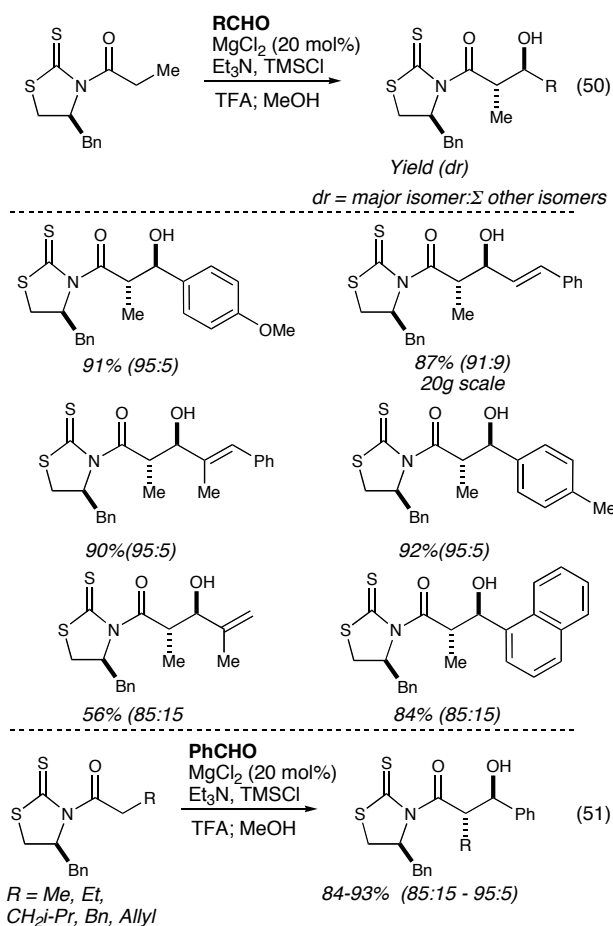
The magnesium-catalyzed aldol process likely involves soft enolization as the key step towards step of the catalytic process (Scheme 13). A control experiment demonstrated that the resultant magnesium enolate does not react with chlorotrimethyl silane to form the silylketene acetal **112**. In addition, the silylketene acetal was prepared separately and shown not to proceed to product under the reactions conditions, thus ruling out a Mukaiyama aldol-type process. Finally, though we do not have detailed kinetic data, it appears that silylation of aldolate **110** is slightly faster than retro-aldol reaction and that the *anti* diastereomer is silylated in preference to the *syn* isomer. We believe that (*Z*)-enolate **109** is formed preferentially, in analogy to the same process with boron, titanium

or tin. Thus, the observed product is formed *via* boat-like transition state **112** which was found to be lower in energy than the corresponding chair-like arrangement which leads to the *syn* isomer.



Scheme 13. Proposed catalytic cycle for the magnesium halide-catalyzed aldol reaction.

The magnesium catalyzed aldol reaction exhibits a stereochemical reversal when chiral thiazolidinethiones are employed (eqs 50 and 51).⁷⁴ Under nearly identical conditions as those used for oxazolidinones, thiazolidinethiones show slightly lower anti diastereoselection, but opposite induction with respect to the auxiliary. Substrate scope is similar and there seem to be no major mechanistic differences. Differential binding to the magnesium center in the transition state is likely responsible for the turnover in selectivity.

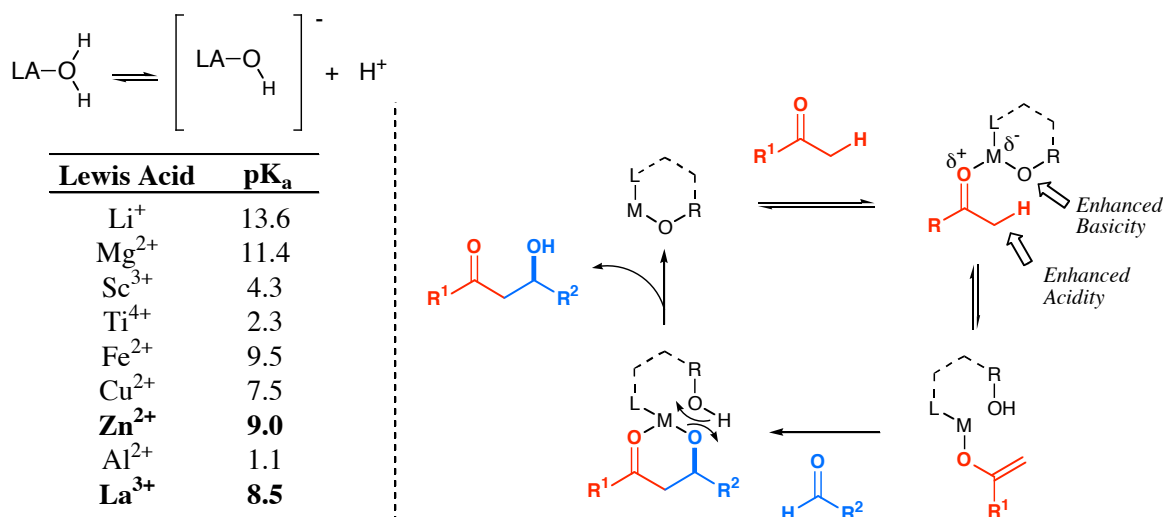


Aldol reactions through soft enolization with magnesium are the newest reactions to be developed. The aldol reactions of oxazolidinones and thiazolidinethiones are the only reactions yet to be made catalytic in the metal source. The extreme cost-effectiveness of the metal source and the viability of these reactions without regard to rigorously dry solvents or purified reagents makes them ideal for large scale production of chiral building blocks. The advent of the magnesium halide-catalyzed aldol reactions portends new reaction advancements in a field already rich with useful developments for several decades.

V. Catalytic Soft Enolization: The Direct Aldol Reaction

While soft enolization generally involves stoichiometric quantities of a metal, several aldol reactions employing metal complexes as catalysts have recently been developed. Many of the catalysts employ transition metal or lanthanide alkoxides. Kobayashi has shown that water bound to a Lewis acidic metal center exhibits

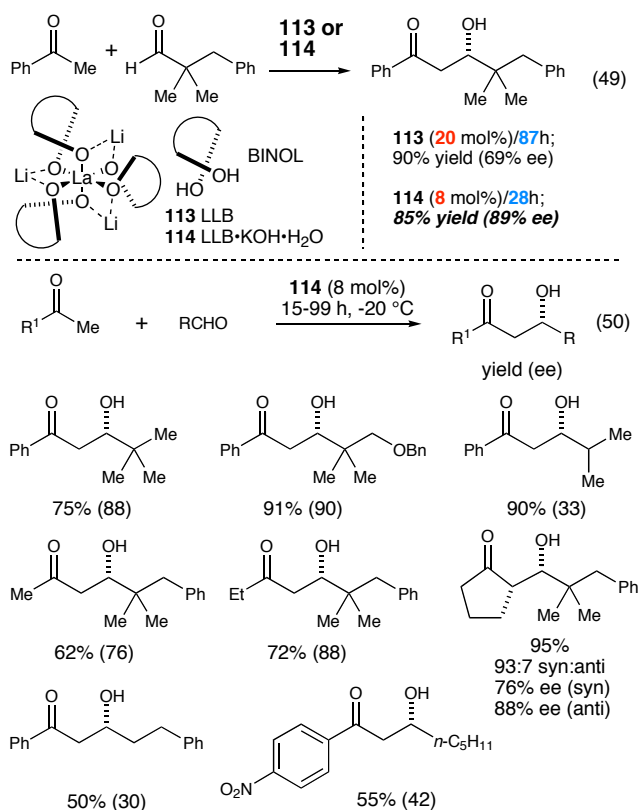
greatly enhanced acidity,⁷⁵ which conversely demonstrates that the resultant metal alkoxides exhibit greatly reduced basicity. Thus, the transition metal and lanthanide alkoxides that have proven to be effective aldol catalysts likely involve soft enolization as a means of forming enolate intermediates. It is reasonable to propose that binding of a carbonyl group acidifies the alpha protons of the enolate donor such that deprotonation by a proximal alkoxide ensues. In most cases, catalysts are homo- or hetero-bimetallic complexes with polyanionic ligands, so one can only speculate on the mechanism of the enolization or subsequent aldol reaction. However, the attenuated basicity of transition metal and lanthanide hydroxides suggests that binding of the Lewis acidic metal center to the carbonyl group is required for enolization.



Scheme 16: Measured acidity of water bound to various Lewis Acidic metal centers (water). Proposed enolate formation by soft enolization with a metal alkoxide.

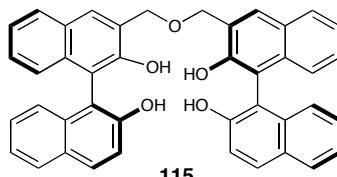
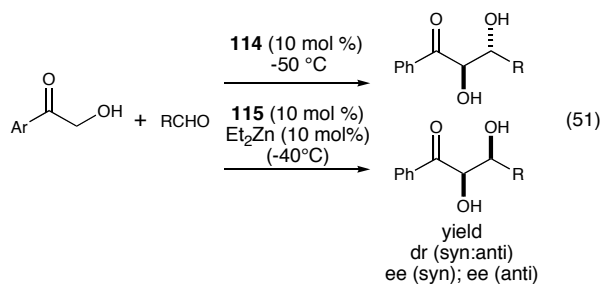
Shibasaki first observed a selective direct aldol reaction⁷⁶ with the LLB (lanthanum-lithium-BINOL) complex **223a** which had proven effective in related Michael and nitroaldol (Henry) reactions.⁷⁷ The parent catalyst provides aldol products from a variety of aldehydes and ketones, but functioned best in the reaction of acetophenone with a sterically encumbered non-enolizable aldehydes. While the first generation catalyst **223a** was a breakthrough for the direct aldol reaction, yields were variable (43-90%), selectivities were substrate-dependent (44-90%), and reaction times were universally

long (3–11 days). An improved catalyst was found when KHMDS and water were incorporated into the catalyst preparation, providing a complex consisting of **223b**, KOH, and H₂O in equimolar ratios.⁷⁸ The new catalyst reduced reaction times, and generally improved the enantioselectivities. While Shibasaki's direct aldol reaction lacks generality, it demonstrated for the first time that practical yields and selectivities could be achieved in the direct aldol reaction.⁷⁹

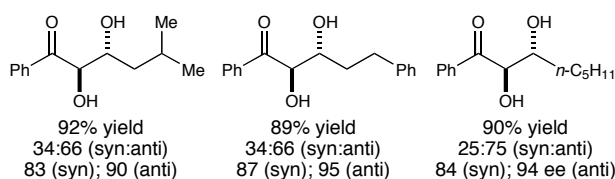


Shibasaki later reported syn- and anti-selective direct aldol reaction of hydroxyacetophenone.⁸⁰ The second generation LLB catalyst **114** is an effective catalyst for the anti-selective direct aldol reactions using enolizable aldehydes. While the diastereoselectivity is modest (66:34–85:15 syn:anti), reaction times are shorter and the ee's higher than those observed for acetophenone. A syn-selective reaction was found when the LLB catalyst **114** was replaced with bimetallic zinc complex **115**. The yields and diastereoselectivities of the syn aldol products were comparable to those observed for the anti-selective reaction, but the enantioselectivities were generally lower. The use of 2-methoxy hydroxyacetophenone as the enolate donor

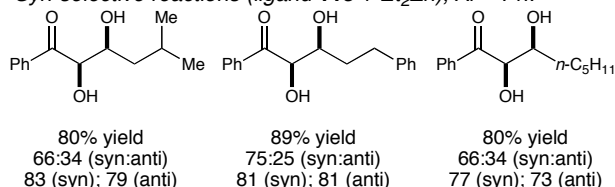
increased yields (83-95%), diastereoselectivities (86:14-97:3) and enantioselectivities (87-98%) of every substrate investigated.⁸¹



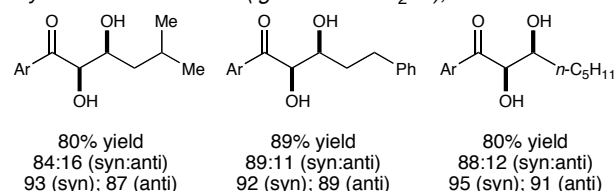
Anti-selective reactions (catalyst 114):



Syn-selective reactions (ligand 115 + Et₂Zn), Ar = Ph:

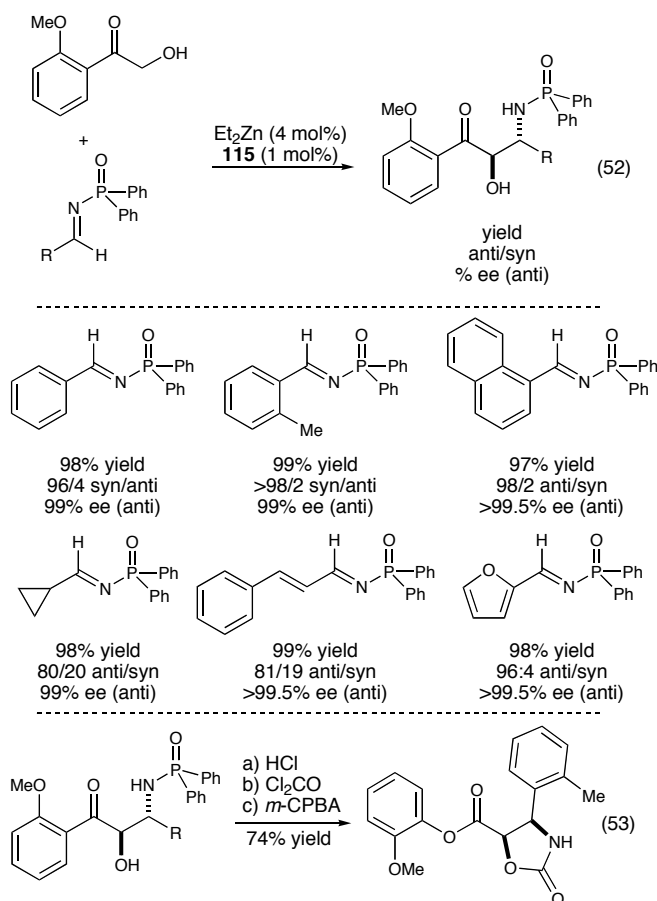


Syn-selective reactions (ligand 115 + Et₂Zn), Ar = 2-MeO-Ph:



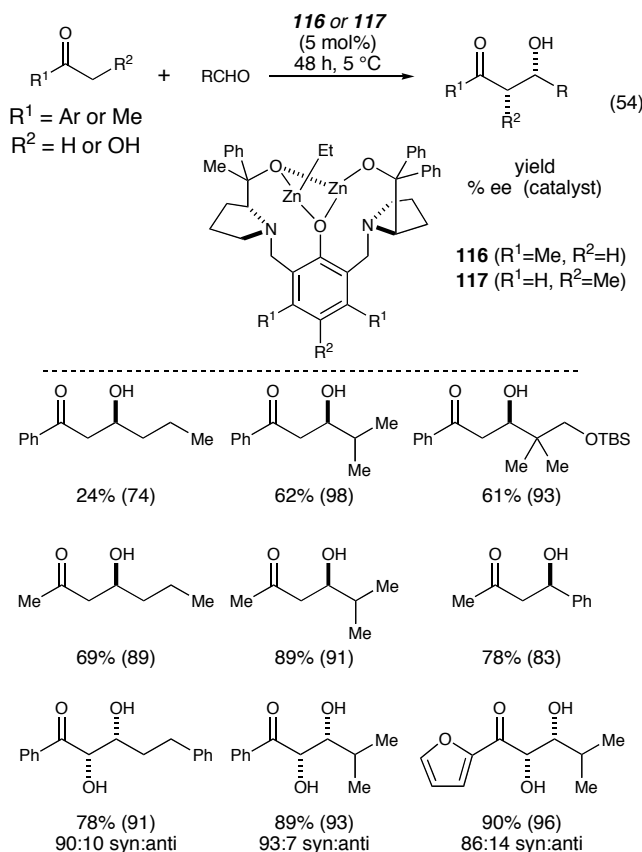
Shibasaki has also reported a zinc complex related to **115** that catalyzes a Mannich reaction in high yield and with enantio- and diastereoselectivity (eq 52).⁸² While the aldol catalyst employs the linked BINOL ligand **115** and Et₂Zn in a 1:2 ratio, a 1:4 ratio is required for the Mannich catalyst. The scope of the reaction is limited to one aryl hydroxymethyl ketone and diphenylphosphinyl imines derived from non-enolizable aldehydes. Aryl aldehyde-derived imines exhibit high (>94:6) selectivity for the anti diastereomer, which cyclopropane carboxaldehyde- and cinnamaldehyde-derived imines show reduced selectivity. While substrate scope is fairly narrow,

the universally high yields and enantiomeric excesses are impressive. In addition, the diphenylphosphinamide products are converted to α -hydroxy- β -amino acid derivatives in high yield (eq 53).



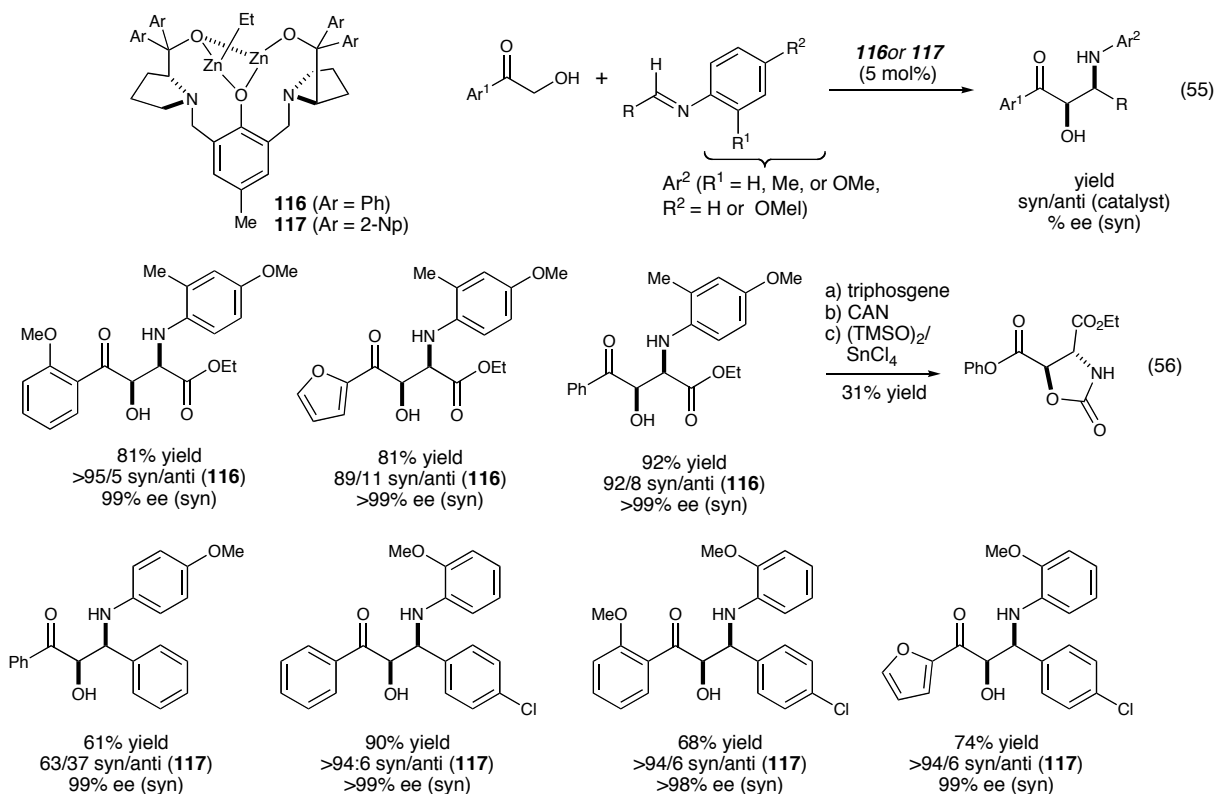
Efficient direct aldol catalysts were recently developed by Trost (eqs 4–6). Bimetallic zinc complexes **234a** and **234b**, with bridging alkoxides are reminiscent of Shibasaki's catalyst **226** and give exceptionally high ee with only 5 mol% catalyst loading for aryl methyl ketones (**235a–e**). Reaction times are shorter than those observed by Shibasaki, though Trost's yields (24–79%) are typically more variable.⁸³ The addition of triphenylphosphine sulfide as a co-catalyst was found to be crucial in many cases, though its role has not been elucidated. The catalyst functions less effectively for acetone (**235f–i**), giving lower enantioselectivity and reduced yield in some cases due to aldol condensation.⁸⁴ Optimal conditions for acetone often required 10 mol% catalyst. High diastereoselectivities (75:25 to >95:5) and yields (62–97%) are observed for hydroxymethyl aryl ketones (**235j–o**), with ee's usually

exceeding 90%.⁸⁵ In the case of these substrates, it is interesting that *lowering* the catalyst loading to 2.5 mol% increased the diastereomeric ratios while only slightly lowering the yield. Despite the lack of mechanistic data and limited substrate scope, the outstanding selectivity and activity of Trost's aldol catalysts are notable.

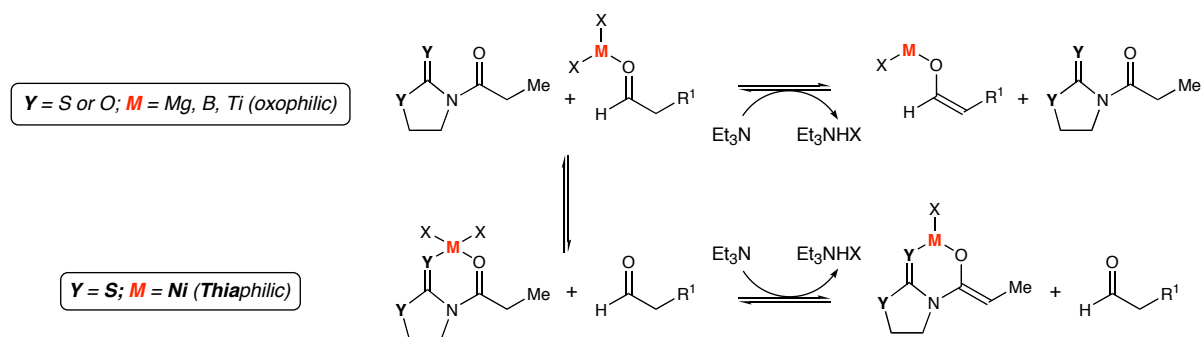


Trost's zinc complex **117** was also shown to catalyze a Mannich reaction (eq 55).⁸⁶ Almost concurrently with Shibasaki's report, Trost reported enantio- and diastereoselective reactions of hydroxy-methyl ketones with diaryl imines. The reaction performs well with glyoxylate- and chlorobenzene-derived imines, and in each case the reaction required an optimal combination of the substituents on the imine and the aryl appendages on the catalyst. The enantioselectivity is consistently above 98%, even in cases where the yield and diastereoselectivity suffer. Interestingly, the absolute configuration of the newly formed *N*-substituted stereogenic center is *opposite* to that observed in the aldol reactions. Unlike Shibasaki, Trost observes high selectivity for the syn diastereomer. One of the

ketone products was converted to the corresponding α -hydroxy- β -amino ester derivative in 3 steps and 31% yield (eq 56).

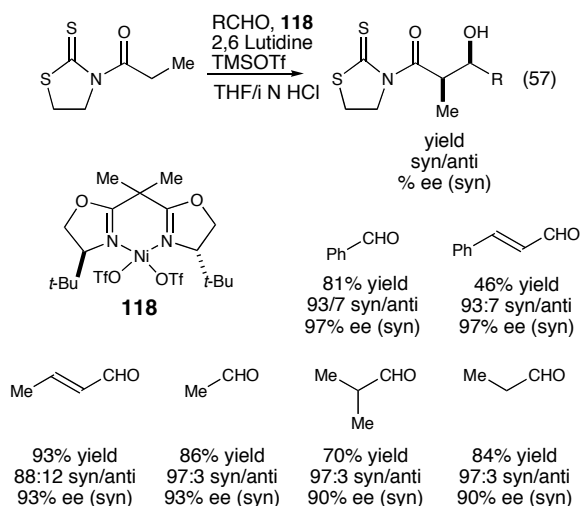


Our group recently developed the first catalytic enantioselective direct aldol process employing carboxylic acid-derived enolate donors. Our magnesium-catalyzed reaction with oxazolidinones exhibited high selectivity and conversion for non-enolizable aldehydes, but alkyl aldehydes were consumed by self-condensation processes under the reaction conditions. We hypothesized that this problem would be eliminated by a more selective enolization process that would favor enolization of the enolate donor over the aldehyde. We found that chelation of oxophilic metal centers by the oxazolidinone or thiazolidinethione was insufficient to direct enolization away from enolizable aldehydes. Conversely, chelation of a thiophilic metal center by thiazolidine thione proved to be an effective strategy, and did lead to an efficient aldol process.



Scheme 17: Selective enolization of a thiazolidinethione by a thiaphilic metal center (nickel).

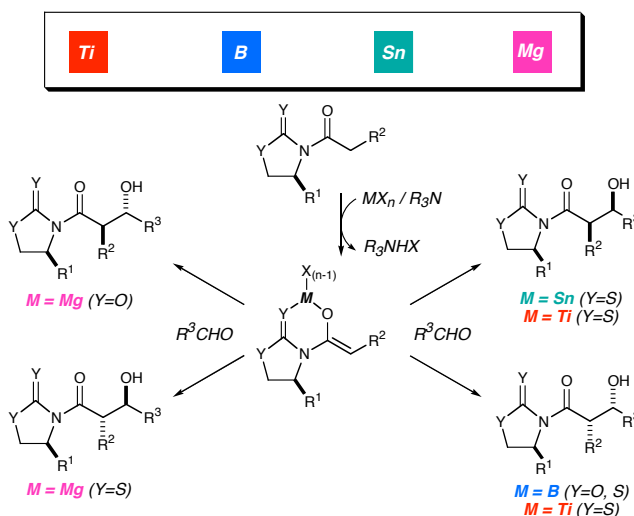
The nickel-catalyzed aldol reaction worked efficiently in the presence of chiral ligands, and thus provided enantiomerically pure aldol products in high yield.⁸⁷ The reaction conditions are similar to the magnesium-catalyzed reaction and efficient turnover is observed only in the process of a stoichiometric quantity of a silylating agent. In this case, $Ni(OTf)_2$ proved to be the optimal metal source. TMSOTf was employed in place of $TMSCl$ to prevent accumulation of $NiCl_2$, since $NiCl_2$ is not sufficiently Lewis acidic to induce enolization. This is the only direct aldol reaction to date that exhibits high diastereoselectivity for propionyl substrates, and the products are easily converted to a variety of useful synthetic precursors.



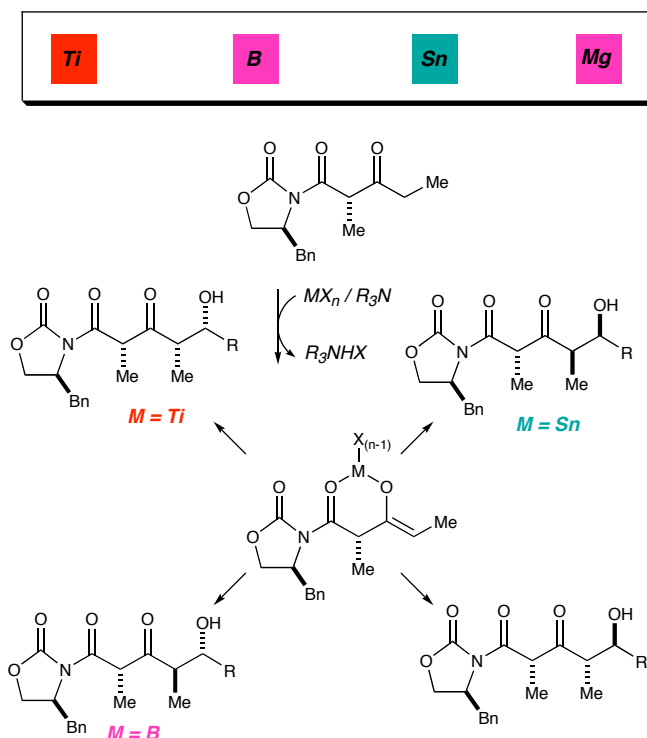
VI. Summary

Soft enolization is a mild and selective method for generating reactive enolates that display complimentary reactivity based on the

choice of metal. Through proper selection of reaction conditions, a wide variety of reaction types are available. In many of the cases discussed, reversals of selectivity are observed when the metal employed for enolization is altered between titanium, boron, tin and magnesium. In the case of the aldol reaction, all possible diastereomers of aldol product are now available from the same enantiomer of chiral auxiliary. This high level of reaction diversity is only possible through modulation of metal binding by proper choice of soft enolization conditions.



Similarly, the β -keto imide aldol reaction shows wide divergence in stereochemical outcome based on the choice of metal. The selective enolization of the less acidic proton of the dicarbonyl compound is only possible through soft enolization. To date, three of the four possible diastereomers are available. In each case, the metal that is employed induces a different mode of binding in the transition state that leads to the observed diastereomer. The β -keto imide aldol reaction has found many applications in the iterative assembly of polypropionate synthons.



Soft enolization is a powerful method that allows the rapid assembly of complex molecular targets under mild conditions. New technology has steadily evolved over the last 25 years to yield predictable trends in reactivity and selectivity that facilitate the complimentary performance of various metal enolates. While the asymmetric aldol reaction exemplifies the reactivity divergence that is made possible through differential binding of the four different metal enolates discussed, many other selective reaction manifolds are emerging. The most active field of reaction development involves the catalytic generation of metal enolates and new selective reactions in this area will continue to be developed.

References:

- [1] (a) C. H. Heathcock, *Science (Washington, D. C., 1883-)* **1981**, 214, 395-400. (b) D. A. Evans, J. V. Nelson, T. R. Taber, *Top. Stereochem.* **1982**, 13, 1-115.
- [2] (a) C. R. Hauser, B. E. Hudson, Jr., *Organic Reactions* **1942**, 1, 266-302. (b) C. R. Hauser, F. W. Swamer, J. T. Adams, *Organic Reactions* **1954**, 8, 59-196.
- [3] Though the first use of a metal-amide base is difficult to assign, Rochow observed formation of lithium enolates using $\text{LiN}(\text{SiMe}_3)_2$: C. R. Krueger, E. G. Rochow, *Angew. Chem.* **1963**, 75, 793.
- [4] J. Ren, C. J. Cramer, R. R. Squires, *J. Am. Chem. Soc.* **1999**, 121, 2633.
- [5] House has examined the stereochemical outcome of a variety of metal enolates through transmetallation with metal salts: H. O. House, D. S. Crumrine, A. Y. Teranishi, H. D. Olmstead, *J. Amer. Chem. Soc.* **1973**, 95, 3310-24. Also, Kennedy recently reported reactions involving the direct generation of magnesium enolates with $\text{Mg}(\text{N}(\text{SiMe}_3)_2)_2$: (a) J. F. Allan, K. W. Henderson, A. R. Kennedy, *Chemical Communications (Cambridge)* **1999**, 1325-1326. (b) J. F. Allan, K. W. Henderson, A. R. Kennedy, S. J. Teat, *Chemical Communications (Cambridge)* **2000**, 1059-1060.
- [6] The model of Zimmerman and Traxler was proposed to explain the outcome of the Reformatsky reaction, which nominally involves a Zn enolate: H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, 79, 1920-1923. This model was later adapted to explain the reactions of E and Z lithium enolates and, with minor modification, most metal enolates described in this review.
- [7] W. Lehnert, *Tetrahedron Lett.* **1970**, 11, 4723-4724.
- [8] C. R. Harrison, *Tetrahedron Lett.* **1987**, 28, 4135-4138.
- [9] Mark E. Bilodeau, Ph.D. dissertation, Harvard University, 1992.
- [10] (a) Y. Xiang, E. Olivier, N. Ouimet, *Tetrahedron Lett.* **1992**, 33, 457-460. Tanabe has made some interesting observations with the enolization of esters with TiCl_4 : (b) Y. Tanabe, *Bull. Chem. Soc. Jpn.* **1989**, 62, 1917-1924. (c) Tanabe, N. Matsumoto, S. Funakoshi, N.

- Manta, *Synlett* **2001**, 1959-1961. (d) Y. Yoshida, R. Hayashi, H. Sumibara, Y. Tanabe, *Tetrahedron Lett.* **1997**, 38, 8727-8730. (e) Y. Yoshida, N. Matsumoto, R. Hamasaki, Y. Tanabe, *Tetrahedron Lett.* **1999**, 40, 4227-4230.
- [11] D. A. Evans, M. T. Bilodeau, T. C. Somers, J. Clardy, D. Cherry, Y. Kato, *J. Org. Chem.* **1991**, 56, 5750-5752.
- [12] D. A. Evans, F. Urpi, T. C. Somers, J. S. Clark, M. T. Bilodeau, *J. Am. Chem. Soc.* **1990**, 112, 8215-8216.
- [13] (a) A. Cosp, P. Romea, P. Talavera, F. Urpi, J. Vilarrasa, M. Font-Bardia, X. Solans, *Org. Lett.* **2001**, 3, 615-617. (b) A. Cosp, P. Romea, F. Urpi, J. Vilarrasa, *Tetrahedron Lett.* **2001**, 42, 4629-4631.
- [14] D. A. Evans, D. L. Rieger, M. T. Bilodeau, F. Urpi, *J. Am. Chem. Soc.* **1991**, 113, 1047-1049.
- [15] (a) M. T. Crimmins, B. W. King, E. A. Tabet, *J. Am. Chem. Soc.* **1997**, 119, 7883-7884. (b) M. T. Crimmins, K. Chaudhary, *Org. Lett.* **2000**, 2, 775-777.
- [16] M. T. Crimmins, B. W. King, E. A. Tabet, K. Chaudhary, *J. Org. Chem.* **2001**, 66, 894-902.
- [17] T. H. Yan, C. W. Tan, H. C. Lee, H. C. Lo, T. Y. Huang, *J. Am. Chem. Soc.* **1993**, 115, 2613-2621.
- [18] A. K. Ghosh, M. Onishi, *J. Am. Chem. Soc.* **1996**, 118, 2527-2529
- [19] A. K. Ghosh, J.-H. Kim, *Org. Lett.* **2003**, 5, 1063-1066.
- [20] (a) T.-H. Yan, A.-W. Hung, H.-C. Lee, C.-S. Chang, *J. Org. Chem.* **1994**, 59, 8187-8191. (b) T.-H. Yan, A.-W. Hung, H.-C. Lee, C.-S. Chang, W.-H. Liu, *J. Org. Chem.* **1995**, 60, 3301-3306.
- [21] N. R. Guz, A. J. Phillips, *Org. Lett.* **2002**, 4, 2253-2256.
- [22] D. A. Evans, J. S. Clark, R. Metternich, V. J. Novack, G. S. Sheppard, *J. Am. Chem. Soc.* **1990**, 112, 866-868.
- [23] D. A. Evans, M. D. Ennis, T. Le, N. Mandel, G. Mandel, *J. Am. Chem. Soc.* **1984**, 106, 1154-1156.
- [24] (a) D. A. Evans, A. S. Kim, *J. Am. Chem. Soc.* **1996**, 118, 11323-11324. (b) D. A. Evans, A. S. Kim, R. Metternich, V. J. Novack, *J. Am. Chem. Soc.* **1998**, 120, 5921-5942.
- [25] T. Mukaiyama, T. Inoue, *Chem. Lett.* **1976**, 559. Many of Mukaiyama's contributions are summarized in the following review: T. Mukaiyama, *Tetrahedron* **1999**, 55, 8609.

- [26] (a) D. A. Evans, E. Vogel, J. V. Nelson, *J. Am. Chem. Soc.* **1979**, *101*, 6120-6123. (b) D. A. Evans, J. V. Nelson, E. Vogel, T. R. Taber, *J. Am. Chem. Soc.* **1981**, *103*, 3099-3111.
- [27] For examples of reaction employing PhBCl, see: (a) H. Hamana, K. Sasakura, T. Sugasawa, *Chem. Lett.* **1984**, 1729-1732. (b) D. A. Evans, M. A. Calter, *Tetrahedron Lett.* **1993**, *34*, 6871-6874. For an example with BCl₃, see: H. F. Chow, D. Seebach, *Helv. Chim. Acta* **1986**, *69*, 604-614.
- [28] H. Hamana, T. Sugasawa, *Chem. Lett.* **1983**, 333-336.
- [29] H. Hamana, T. Sugasawa, *Heterocycles* **1984**, *21*, 534.
- [30] H. Hamana, T. Sugasawa, *Chem. Lett.* **1984**, 1591-1594. For a related process with nitriles, see: H. Hamana, T. Sugasawa, *Chem. Lett.* **1982**, 1401-1404.
- [31] (a) H. C. Brown, R. K. Dhar, R. K. Bakshi, P. K. Pandiarajan, B. Singaram, *J. Am. Chem. Soc.* **1989**, *111*, 3441-3442. (b) H. C. Brown, K. Ganesan, R. K. Dhar, *J. Org. Chem.* **1992**, *57*, 3767-3772. For related observations with esters, see: A. Abiko, J.-F. Liu, S. Masamune, *J. Org. Chem.* **1996**, *61*, 2590-2591.
- 32[1] A. Abiko, J.-F. Liu, S. Masamune, *J. Org. Chem.* **1996**, *61*, 2590.
- 33 (a) A. Abiko, J.-F. Liu, S. Masamune, *J. Am. Chem. Soc.* **1997**, *119*, 2586. (b) J.-F. Liu, A. Abiko, Z. Pei, D. C. Buske, S. Masamune, *Tetrahedron Lett.* **1998**, *39*, 1873. (c) T. Inoue, J.-F. Liu, D. C. Buske, A. Abiko, *J. Org. Chem.* **2002**, *67*, 5250.
- 34 A. Abiko, J.-F. Liu, D. C. Buske, S. Moriyama, S. Masamune, *J. Am. Chem. Soc.* **1999**, *121*, 7168.
- [35] A subsequent report describes the asymmetric reaction of acetyl oxazolidinones: H. Furuno, T. Inoue, A. Abiko, *Tetrahedron Lett.* **2002**, *43*, 8297.
- [36] (a) A. Abiko, T. Inoue, H. Furuno, H. Schwalbe, C. Fieres, S. Masamune, *J. Am. Chem. Soc.* **2001**, *123*, 4605.
- [37] (a) A. Abiko, T. Inoue, S. Masamune, *J. Am. Chem. Soc.* **2002**, *124*, 10759.
- [38] (a) D. A. Evans, B. W. Trotter, B. Cote, P. J. Coleman, L. C. Dias, A. N. Tyler, *Angew. Chem., Int. Ed. Engl.* **1998**, *36*, 2744-2747. (b) D. A. Evans, P. J. Coleman, L. C. Dias, *Angew. Chem., Int. Ed. Engl.* **1998**, *36*, 2738-2741. (c) D. A. Evans, B. W. Trotter, B. Cote,

- P. J. Coleman, *Angew. Chem., Int. Ed. Engl.* **1998**, *36*, 2741-2744. (d) D. A. Evans, B. W. Trotter, P. J. Coleman, B. Cote, L. C. Dias, H. A. Rajapakse, A. N. Tyler, *Tetrahedron* **1999**, *55*, 8671-8726.
- [39] D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.
- [40] (a) H. Danda, M. M. Hansen, C. H. Heathcock, *J. Org. Chem.* **1990**, *55*, 173-181. (b) H. Danda, M. M. Hansen, C. H. Heathcock, *J. Org. Chem.* **1990**, *55*, 6231. (c) M. A. Walker, C. H. Heathcock, *J. Org. Chem.* **1991**, *56*, 5747-5750. (d) B. C. Raimundo, C. H. Heathcock, *Synlett* **1995**, 1213-1214.
- [41] D. A. Evans, T. C. Britton, J. A. Ellman, R. L. Dorow, *J. Am. Chem. Soc.* **1990**, *112*, 4011-4030.
- [42] (a) D. A. Evans, T. C. Britton, R. L. Dorow, J. F. Dellaria, *J. Am. Chem. Soc.* **1986**, *108*, 6395-6397. (b) D. A. Evans, T. C. Britton, *J. Am. Chem. Soc.* **1987**, *109*, 6881-6883. (c) D. A. Evans, T. C. Britton, J. A. Ellman, R. L. Dorow, *J. Am. Chem. Soc.* **1990**, *112*, 4011-4030.
- [43] (a) D. A. Evans, E. B. Sjogren, A. E. Weber, R. E. Conn, *Tetrahedron Lett.* **1987**, *28*, 39-42. (b) D. A. Evans, J. A. Ellman, R. L. Dorow, *Tetrahedron Lett.* **1987**, *28*, 1123-1126.
- [44] D. A. Evans, A. E. Weber, *J. Am. Chem. Soc.* **1987**, *109*, 7151-7157.
- [45] D. A. Evans, H. P. Ng, J. S. Clark, D. L. Rieger, *Tetrahedron* **1992**, *48*, 2127-2142.
- [46] (a) D. A. Evans, V. J. Cee, T. E. Smith, D. M. Fitch, P. S. Cho, *Angew. Chem., Int. Ed.* **2000**, *39*, 2533-2536. (b) D. A. Evans, D. M. Fitch, *Angew. Chem., Int. Ed.* **2000**, *39*, 2536-2540. (c) D. A. Evans, D. M. Fitch, T. E. Smith, V. J. Cee, *J. Am. Chem. Soc.* **2000**, *122*, 10033-10046.
- [47] (a) T. Mukaiyama, R. W. Stevens, N. Iwasawa, *Chem. Lett.* **1982**, 353-356. For a review, see: (b) T. Mukaiyama, S. Kobayashi, *Org. React. (N. Y.)* **1994**, *46*, 1-103.
- [48] T. Mukaiyama, N. Iwasawa, *Chem. Lett.* **1982**, 1903-1906.
- [49] (a) N. Iwasawa, H. Huang, T. Mukaiyama, *Chem. Lett.* **1985**, 1045-1048. (b) N. Iwasawa, T. Mukaiyama, *Chem. Lett.* **1986**, 637-640.

- [50] (a) [1] N. Iwasawa, T. Mukaiyama, *Chem. Lett.* **1983**, 297-298. (b) R. W. Stevens, T. Mukaiyama, *Chem. Lett.* **1983**, 1799-1802. (c) T. Mukaiyama, N. Iwasawa, *Chem. Lett.* **1984**, 753-756.
- [51] (a) Y. Nagao, S. Yamada, T. Kumagai, M. Ochiai, E. Fujita, *J. Chem. Soc., Chem. Commun.* **1985**, 1418-1419. (b) Y. Nagao, T. Inoue, K. Hashimoto, Y. Hagiwara, M. Ochiai, E. Fujita, *J. Chem. Soc., Chem. Commun.* **1985**, 1419-1420.
- [52] Y. Nagao, Y. Hagiwara, T. Kumagai, M. Ochiai, T. Inoue, K. Hashimoto, E. Fujita, *J. Org. Chem.* **1986**, 51, 2391-2393.
- [53] R. C. D. Brown, P. J. Kocienski, *Synlett* **1994**, 415-417.
- [54] A. N. Cuzzupe, C. A. Hutton, M. J. Lilly, R. K. Mann, M. A. Rizzacasa, S. C. Zammit, *Org. Lett.* **2000**, 2, 191-194.
- [55] D. Zuev, L. A. Paquette, *Org. Lett.* **2000**, 2, 679-682.
- [56] (a) Y. Nagao, T. Kumagai, S. Tamai, T. Abe, Y. Kuramoto, T. Taga, S. Aoyagi, Y. Nagase, M. Ochiai, et al., *J. Am. Chem. Soc.* **1986**, 108, 4673-4675. (b) Y. Nagao, T. Kumagai, T. Abe, M. Ochiai, T. Taga, K. Machida, Y. Inoue, *J. Chem. Soc., Chem. Commun.* **1987**, 602-603. (c) Y. Nagao, T. Abe, H. Shimizu, T. Kumagai, Y. Inoue, *J. Chem. Soc., Chem. Commun.* **1989**, 821-823. (d) [1] Y. Nagao, T. Kumagai, Y. Nagase, S. Tamai, Y. Inoue, M. Shiro, *J. Org. Chem.* **1992**, 57, 4232-4237. (e) Y. Nagao, Y. Nagase, T. Kumagai, Y. Kuramoto, S. Kobayashi, Y. Inoue, T. Taga, H. Ikeda, *J. Org. Chem.* **1992**, 57, 4238-4242. (f) Y. Nagao, Y. Nagase, T. Kumagai, H. Matsunaga, T. Abe, O. Shimada, T. Hayashi, Y. Inoue, *J. Org. Chem.* **1992**, 57, 4243-4249.
- [57] (a) Y. Nagao, W. M. Dai, M. Ochiai, S. Tsukagoshi, E. Fujita, *J. Am. Chem. Soc.* **1988**, 110, 289-291. (b) Y. Nagao, W. M. Dai, M. Ochiai, S. Tsukagoshi, E. Fujita, *J. Org. Chem.* **1990**, 55, 1148-1156.
- [58] (a) Y. Nagao, W. M. Dai, M. Ochiai, *Tetrahedron Lett.* **1988**, 29, 6133-6136. (b) Y. Nagao, W. M. Dai, M. Ochiai, M. Shiro, *Tetrahedron* **1990**, 46, 6361-6380.
- [59] D. A. Evans, J. R. Gage, J. L. Leighton, A. S. Kim, *J. Org. Chem.* **1992**, 57, 1961-1963. Brimble et al used a similar reaction in their synthesis of Griseusin analogs: M. A. Brimble, M. R. Nairn, J. Park, *Org. Lett.* **1999**, 1, 1459-1462.
- [60] A. Abdel-Magid, L. N. Pridgen, D. S. Eggleston, I. Lantos, *J. Am. Chem. Soc.* **1986**, 108, 4595-4602.
- [61] D. L. Boger, T. Honda, *Tetrahedron Lett.* **1993**, 34, 1567-1570.

-
- [62] D. A. Evans, A. E. Weber, *J. Am. Chem. Soc.* **1986**, *108*, 6757-6761.
- [63] D. A. Evans, M. R. Wood, B. W. Trotter, T. I. Richardson, J. C. Barrow, J. L. Katz, *Angew. Chemie, Int. Ed.* **1998**, *37*, 2700-2704.
- [64] D. A. Evans, A. M. Ratz, B. E. Huff, G. S. Sheppard, *J. Am. Chem. Soc.* **1995**, *117*, 3448-3467.
- [65] (a) [1] R. E. Tirpak, R. S. Olsen, M. W. Rathke, *J. Org. Chem.* **1985**, *50*, 4877-4879. (b) R. S. Olsen, Z. A. Fataftah, M. W. Rathke, *Synth. Commun.* **1986**, *16*, 1133-1139. (c) R. E. Tirpak, R. S. Olsen, M. W. Rathke, *J. Org. Chem.* **1985**, *50*, 4877-4879.
- [66] W. L. Driessen, P. L. A. Everstijn, *Inorg. Chim. Acta* **1980**, *41*, 179-183.
- [67] C. Kashima, K. Takahashi, K. Fukusaka, *J. Heterocycl. Chem.* **1995**, *32*, 1775-1777.
- [68] C. Kashima, I. Fukuchi, K. Takahashi, K. Fukusaka, A. Hosomi, *Heterocycles* **1998**, *47*, 357-365.
- [69] C. Kashima, K. Fukusaka, K. Takahashi, *Journal of Heterocyclic Chemistry* **1997**, *34*, 1559-1565.
- [70] K. Hayashi, H. Kogiso, S. Sano, Y. Nagao, *Synlett* **1996**, 1203-1205.
- [71] Mark E. Bilodeau, Ph.D. dissertation, Harvard University, 1992.
- [72] (a) A. Furstner, N. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 12349-12357. (b) A. Furstner, *Pure and Applied Chemistry* **1998**, *70*, 1071-1076. (c) A. Furstner, *Chemistry--A European Journal* **1998**, *4*, 567-570.
- [73] D. A. Evans, J. S. Tedrow, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2002**, *124*, 392-393.
- [74] D. A. Evans, C. W. Downey, J. T. Shaw, J. S. Tedrow, *Org. Lett.* **2002**, *4*, 1127-1130.
- [75] S. Kobayashi, S. Nagayama, T. Busujima, *J. Am. Chem. Soc.* **1998**, *120*, 8287.
- [76] Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871.
- [77] Recent reviews include: (a) M. Shibasaki, M. Kanai, K. Funabashi, *Chem. Comm.* **2002**, 1989. (b) S. Matsunaga, T. Ohshima, M. Shibasaki, *Advanced Synthesis & Catalysis* **2002**, *344*, 3. (c) M. Shibasaki, *Enantiomer* **1999**, *4*, 513. (d) M. Shibasaki, H. Sasai, T.

Arai, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1237. (e) M. Shibasaki, H. Sasai, *Pure and Applied Chemistry* **1996**, *68*, 523.

[78] N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 4168.

[79] Though largely overlooked, the first example of a metal-catalyzed asymmetric direct aldol reaction was reported by Watanabe: (a) M. Nakagawa, H. Nakao, K. Watanabe, *Chem. Lett.* **1985**, 391. (b) Y. Yamada, K. Watanabe, H. Yasuda, *Utsunomiya Daigaku Kyoikugakubu Kiyo, Dai-2-bu* **1989**, *39*, 25. Several other direct metal-catalyzed aldol processes have been reported in which a base is not used or is not required for conversion: (a) TiCl_4 : R. Mahrwald, B. Guendogan, *J. Am. Chem. Soc.* **1998**, *120*, 413. (b) InCl_3 : T.-P. Loh, L.-L. Wei, L.-C. Feng, *Synlett* **1999**, 1059. (d) (bisoxazoline) $\text{Cu}(\text{OTf})_2$, dimerization of ethyl pyruvate: K. Juhl, N. Gathergood, K. A. Jorgensen, *Chem. Comm.* **2000**, 2211. (d) (bisoxazoline) $\text{Cu}(\text{OTf})_2$, Mannich reactions: K. Juhl, N. Gathergood, K. A. Jorgensen, *Angew. Chem., Int. Ed.* **2001**, *40*, 2995.

[80] (a) N. Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, T. Ohshima, T. Suzuki, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2466. (b) N. Yoshikawa, T. Suzuki, M. Shibasaki, *J. Org. Chem.* **2002**, *67*, 2556.

[81] N. Kumagai, S. Matsunaga, N. Yoshikawa, T. Ohshima, M. Shibasaki, *Org. Lett.* **2001**, *3*, 1539.

[82] S. Matsunaga, N. Kumagai, S. Harada, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 4712.

[83] B. M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003.

Related complexes also catalyze the nitroaldol (Henry) reaction: (a) B. M. Trost, V. S. C. Yeh, H. Ito, N. Bremeyer, *Org. Lett.* **2002**, *4*, 2621. (b) B. M. Trost, V. S. C. Yeh, *Angew. Chem., Int. Ed.* **2002**, *41*, 861.

[84] B. M. Trost, E. R. Silcoff, H. Ito, *Org. Lett.* **2001**, *3*, 2497.

[85] B. M. Trost, H. Ito, E. R. Silcoff, *J. Am. Chem. Soc.* **2001**, *123*, 3367.

[86] B. M. Trost, L. R. Terrell, *J. Am. Chem. Soc.* **2003**, *125*, 338.

[87] D. A. Evans, C. W. Downey, J. L. Hubbs, *J. Am. Chem. Soc.* **2003**, *125*, 8706.